A COMPARISON OF THREE DIFFERENT DOSES OF MANNITOL ON BRAIN RELAXATION DURING SUPRATENTORIAL BRAIN TUMOR CRANIOTOMY

DISSERTATION SUBMITTED FOR

DOCTOR OF MEDICINE

BRANCH X (ANAESTHESIOLOGY)

April 2015

THE TAMILNADU

DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

CERTIFICATE FROM DIRECTOR & HOD

This is to certify that this dissertation titled "**A COMPARISON OF THREE DIFFERENT DOSES OF MANNITOL ON BRAIN RELAXATION DURING SUPRATENTORIAL BRAIN TUMOR CRANIOTOMY**" is a bonafide record work done by **DR.K.PRASANNA,** under my direct supervision and guidance, submitted to THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY in partial fulfillment of university regulation for **MD, Branch X Anaesthesiology** examination to be held in **April 2015**.

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DECLARATION

I **Dr. K. PRASANNA**, solemnly declare that this dissertation entitled "**A COMPARISON OF THREE DIFFERENT DOSES OF MANNITOL ON BRAIN RELAXATION DURING SUPRATENTORIAL BRAIN TUMOR CRANIOTOMY**" has been done by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, or diploma to any other university or board either in India or abroad. This is submitted to The Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the award of doctor of medicine degree **Branch X – Anaesthesiology** to held in **April 2015.**

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ACKNOWLEDGEMENT

I am greatly indebted to **Dr. S.C. Ganesh prabhu M.D., D.A.,** director and head of the Institute of anaesthesiology, Madurai medical college, Madurai for his guidance and encouragement in preparing this dissertation. My heart full thanks to **Dr. R.Shanmugam, M.D.,D.C.H.,** professor of anaesthesiology, Madurai medical college, Madurai, for his guidance in doing this work.

I also thank my professors **Dr.T.Thirunavukarasu M.D.,D.A., Dr.A.Paramasivanm, M.D.,D.A.,** and **Dr.Evelyn asirvatham., M.D., D.G.O., D.C.H.,** for their constant support and guidance in performing this study.

I also thank my assistant professor **Dr.S.Vijayaragavan M.D.,D.A.,** for his constant support in conducting this study.

My profound thanks to **Captain. Dr.B. SANTHAKUMAR M.Sc., (F.Sc), M.D.,(FM) PGDMLE, DNB (F.M.) Dean,** Madurai medical college and Government Rajaji Hospital in the completion of my dissertation.

I grateful acknowledge the **patients** who gave their consent and cooperation for this study.

CONTENTS

A comparison of three different doses of mannitol on brain relaxation during supratentorial brain tumor craniotomy

Abstract

BACKGROUND: Twenty percent mannitol is widely used to reduce brain bulk and facilitate the surgical approach in intracranial surgery. However, a dose-response relationship has not yet been established. In this study, we compared the effects of 0.5,1.0 and 1.5 $g \cdot kg^{-1}$ mannitol on brain relaxation during elective supratentorial brain tumor surgery.

METHODS: In this prospective, randomized, single -blind study, we enrolled 48 patients undergoing supratentorial craniotomy for tumor resection. Patients were assigned to receive 0.5 $g \cdot kg^{-1}$ (group a), 1.0 $g \cdot kg^{-1}$ (group b) or 1.5 $g \cdot kg^{-1}$ (group c) of 20% mannitol at surgical incision. Brain relaxation was assessed immediately after opening of the dura on a scale(rozet quentin scale) ranging from 1 to 4 (Scale 1: perfectly relaxed (shrunken dura with prominent veins)Scale 2: satisfactorily relaxed (only prominent veins)Scale 3: firm brain, Scale 4: bulging brain).secondary out come measures like mean arterial blood pressure, arterial blood electrolytes, blood PH, urine output and temperature also measured.

RESULTS: There was no significant difference between the 3 groups regarding age, sex, body mass index, and brain tumor localization or size. We then used a proportional odds model to adjust for this unbalanced distribution and to assess the group effect (low-dose versus high-dose mannitol) on brain relaxation scores. Serum electrolytes, blood gases, urine output and hemodynamic stability are better maintained in group c .

CONCLUSION: In this study, from the data and statistical analysis, shows that 1.5g·kg^{-1} of 20% mannitol results in better brain relaxation scores than 0.5 and 1.0 g·kg^{-1} in patients undergoing craniotomy for supratentorial brain tumor. In this study, it is concluded that 1.5mg/kg of 20% mannitol gives better brain relaxation scores with blood electrolytes, blood PH, urine output and hemodynamic stability are better maintained .

Key words: 20% mannitol, relaxation scores, mean arterial pressure, blood electrolytes, urine output, PH, supratentorial brain tumours, craniotomy.

INTRODUCTION

Most of the brain tumors are supratentorial tumors (79%), the most common of which are gliomas, meningiomas, and pituitary tumors. Supratentorial tumors produce significant mass effects in the brain, and certain types are accompanied by significant peritumoral edema that leads to increased intracranial pressure. Bedford et al. showed that the preoperative degree of peritumoral edema was closely related to the postoperative increase in intracranial pressure. Rasmussen et al. revealed that the risk of brain swelling after dura opening was very high in 692 cases of patients with glioma with midline shift undergoing craniotomy; this result indicated that in cases with preoperative increased intracranial pressure, dehydration treatment should be administered before cutting the dura. Dehydration aids in ensuring proper brain relaxation and facilitates tumor exposure. Higher osmotic pressure in the blood vessels after the infusion of mannitol drives water molecules from the brain tissue to blood vessels and results in brain tissue dehydration. However, the role of mannitol in reducing brain edema depends on an intact blood–brain barrier (BBB). If the BBB is damaged, mannitol will extravasate outside the blood vessels and will transfer water molecules into brain tissue, which

will aggravate cerebral edema and increase intracranial pressure. There may be some degree of BBB disruption in certain patients, which would prevent the desirable effects of mannitol; however, the extent of this disruption is unclear and often affected by multiple-dose mannitol. The use of mannitol for the type of surgery that patients in our study will undergo has been found overall to be beneficial; however, the appropriate dose of mannitol is controversial, particularly since large multiple doses can have negative effects. Some clinicians advocate high doses (>1.0 gm/kg) of mannitol to effectively reduce intracranial pressure, while others recommend lower doses (<1.0 gm/kg). But recently clinicians advocate still high dose of mannitol upto 1.5gm/kg to effectively reduce intracranial pressure Treatment guidelines for using mannitol in patients undergoing superatentorial brain tumour craniotomy have been published and provide recommendations regarding the dose and timing of mannitol. However, there is still controversy concerning dehydration treatment with mannitol in patients with preoperatively increased intracranial pressure during brain tumor surgery. More recently, a prospective randomized controlled study demonstrated that a single dose of 0.5 gm/kg or 1.4 gm/kg mannitol achieved similar brain relaxation in patients undergoing superatentorail brain tumour craniotomy and tumor

resection. However, further statistical analysis that took into account the preoperative midline shift indicated that the high dose yielded a better outcome. Mannitol and hypertonic saline are often used as dehydrating agents in neurosurgery and neurology. Hypertonic saline has been widely used in patients with stroke and traumatic brain injury to reduce brain edema and intracranial pressure; however, its use, especially during the operation, remains controversial in patients undergoing brain tumor surgery. Starke et al presented a comprehensive assessment of the effect of hypertonic saline during brain tumor resection and did not recommend it as a treatment for dehydration in brain tumor surgery unless the patient presents with hyponatremia and hypotension. Dehydration treatment with mannitol was recommended to reduce brain edema and provide brain relaxation during neurosurgery.

The study indicated that the effect of mannitol on brain relaxation may be dose-dependent if the preoperative increase in intracranial pressure is taken into consideration; however, further study is required to verify this suggestion. The point of my study is to determine a dose that leads to a beneficial effect without triggering negative effects.

AIM OF THE STUDY

PRIMARY AIM OF THE STUDY :

To compare three different doses of 20% mannitol (0.5 gm/kg, 1.0 gm/kg, 1.5gm/kg) on brain relaxation during supratentorial brain tumour craniotomy.

SECONDARY AIM OF THE STUDY :

I. To evaluate change in haemodynamic stability following different doses of mannitol administration.

II. To evaluate change in blood PH following different doses of mannitol administration.

III. To evaluate change in blood electrolytes following different doses of mannitol administration.

ANATOMY AND PHYSIOLOGY OF NEUROLOGICAL COMPENSATORY MECHANISMS

The components of the skull exist in a state of dynamic equilibrium. If one component of the skull is altered, the other components either need to compensate for the change or will be altered themselves.

THE CRANIUM

The cranium is made of an inner and outer table of bone separated by spongy tissue, which helps to maximize strength but allows it to be lightweight as well. The only opening in the skull is the foramen Magnum, ‘‘big hole,’’ located at the base of the skull, through which the spinal cord emerges. The cerebral cortex has a right and a left hemisphere, sitting above the tentorium. ‘‘Like a tent,’’ the tentorium is made of the inner foldings of the dura (outer covering of the brain) which separate the cerebral cortex from each other and the cerebellum. The tentorium helps to absorb downward pressure from the cerebral cortex on the cerebellum and brainstem and provides a physical barrier to the movement of intracerebral structures. The brainstem consists of the midbrain, pons, and medulla, all lying above the foramen Magnum in the skull, making them vulnerable to

compression if increased ICP exists. Cerebral volume consists of 3 components: cerebral tissue, blood, and cerebral spinal fluid (CSF).

MONROE AND KELLIE HYPOTHESIS:

More than two centuries ago, Alexander Monro applied some of the principles of physics to the intracranial contents and for the first time hypothesized that the blood circulating in the cranium was of constant volume at all times. This hypothesis was supported by experiments by Kellie. In its original form, the hypothesis had shortcomings that prompted modification by others. What finally came to be known as the Monro–Kellie doctrine, or hypothesis,

Monro–Kellie doctrine, or hypothesis, is that the sum of volumes of brain, CSF, and intracranial blood is constant. An increase in one should cause a decrease in one or both of the remaining two. This hypothesis has substantial theoretical implications in increased intracranial pressure and in decreased CSF volume.

These mechanisms will be reviewed while looking at cerebral anatomy and physiology. Remember, once neuronal cells become injured, the brains ability to compensate is finite, decompensation can occur rapidly, and damage to the vulnerable adjacent tissues (known as secondary injury) will ensue.

COMPONENTS OF THE SKULL: THE BRAIN

The brain tissue occupies 80% of intracerebral volume, including brain tissue and interstitial and intracellular water. The outermost covering of the brain and the spinal cord is the meninges, ‘‘membranes.’’ The 3 layers of the meninges are the dura mater, the arachnoid membrane, and the pia mater. The dura mater lines the inner table on the skull and is very inelastic. In fact, this strong dural layer has been described by Barbara McLean as the box (dura mater) within a box (the skull), protecting the delicate structures within. The dura mater consists of 2 layers, the periosteal lining and the meningeal lining. Between these 2 layers are sinuses or drainage canals where CSF and venous blood can drain into before exiting the skull. The middle layer of the meninges is called the arachnoid membrane, a translucent, thin, web-like structure, loosely covering the brain and housing circulating CSF. The third and inner most layer of the meninges is the pia mater, adhering to the brain and following all of the gyri (folds) of the brain surface. Between each of the layers of the meninges are spaces or potential spaces. The epidural space lies above the dura and the subdural space is below the dura. Both of these are only potential spaces, and fluid or blood within these space areas would be abnormal. The subarachnoid space (SAS) is below the

arachnoid layer, and normally, only 150 ml of CSF at one time circulates in this actual space around the brain and spinal cord. Within the SAS are small structures called arachnoid villi necessary for reabsorbing CSF into the drainage sinuses or canals. Cerebral spinal fluid will be discussed in greater depth later in this article. The white and gray matter of the brain, or the central nervous system, consists of two types of cerebral cells: the neurons responsible for neurotransmission and the neuroglial cells responsible for providing support and structure to the brain. The neuroglial cells are diverse and complex and were originally described by Dr Virchow, a German physiologist in 1846, as the ''glue of the brain.'' The 2 main categories of neuroglial cells will be addressed here: the microglial cells and the macroglial cells. The microglial cells are the smallest of the glial cells and primarily act as macrophages eliminating debris and serving as the brain's weapon against invading microorganisms. Lying dormant until called into action, these chemical arsenals have the potential to support and/or destroy neuronal tissue. Subtypes of the macroglial cells include oligodendrocytes, astrocytes, and the ependyma cells. The oligodendrocytes are responsible for myelin sheath formation, replacing myelin already destroyed. A second type of macroglial cell is the star-shaped astrocyte. Astrocytes relay nutrients through the

neuronal network, reuptake neurotransmitters such as glutamate, and its unique morphology helps to create the blood-brain barrier (BBB). Brain tissue cannot decrease its mass as a way to compensate for increased intracerebral volume. The brain will need to rely on the other two components of the skull to alter their physical properties to compensate for increasing cerebral volume to prevent increased ICP.

THE COMPONENTS OF THE SKULL

THE BLOOD :

The second component in the skull, blood, occupies 10% of intracranial space. The brain receives a constant supply of blood at a rate of 750 ml/min via two internal carotid arteries and two vertebral arteries.

Compared to other arteries in the body of the same size, the cerebral arterial walls are thinner due to their lack of smooth muscle and decreased media. Normally, these vessels do not need to accommodate high pressures like the rest of the body, nor do they have the ability to develop collateral circulation in response to ischemia. The cerebral arterioles possess the ability to autoregulate their size, dilating and constricting, to increase or decrease cerebral blood flow to meet tissue demands. The cerebral vessels deliver a constant supply of blood

even when there are wide fluctuations in systemic blood pressure. Autoregulation is an automatic compensatory mechanism used to either limit the amount of cerebral volume through vasoconstriction and therefore limit pressure or increase volume through vasodilation when demands for oxygen and blood are greater. The body also responds to increasing cerebral mass by causing spontaneous hyperventilation. The cerebral vasculature responds by vasoconstricting, limiting cerebral blood flow, and ultimately, negatively impacting the delivery of oxygen and glucose to the tissues. This innate compensatory mechanism can worsen ischemia further, but intervening early with mechanical ventilation may decrease the damaging effects of spontaneous hyperventilation and improve cerebral blood flow. The patient suffering from a neurological insult is especially vulnerable to the increased metabolic demands of the injured tissue when supply is low. For example, cerebral blood flow drops by 50% after traumatic brain injury in the first 24 to 48 hours after injury. This, in addition to the potential loss of autoregulation, can seriously compromise cerebral perfusion Cerebral perfusion pressure (CPP) grossly reveals information on cerebral oxygen supply and demand. The measurement of MAP represents flow to the cerebrum and ICP

represents the resistance to the flow. The end product of these 2 forces is CPP (MAP - ICP = CPP).

When CPP falls below 60 mm Hg, cerebral blood flow drops, the ability of the cerebral arteries to autoregulate is impaired, and cerebral blood flow becomes passive. Hypotension has a dramatic effect on mortality related to traumatic brain injury and should be aggressively avoided. Critical care nurses need to intervene when the patient's own compensatory mechanisms fail by supporting hemodynamics and optimizing cerebral perfusion.

THE COMPONENTS OF THE BRAIN

CEREBRO SPINAL FLUID :

The last 10% of what fills the skull is the CSF surrounding the brain and spinal cord in the SAS. Like all fluids, CSF is noncompressible; therefore, it acts as a cushion and support for the brain and spinal cord.

Cerebral spinal fluid is normally produced at a rate of 20 mL/h, but the rate of production depends largely on cerebral blood flow. For example, if cerebral blood flow is decreased because of vasoconstriction via auto regulation, this compensatory response will result in decreased ICP directly due to decreased cerebral blood

volume and indirectly due to decreased production of CSF. Choroid plexi are capillary tufts primarily located in the 2 lateral ventricles responsible for the production of 95% of the CSF. The ependyma cells secrete the CSF into the ventricles. The last 5% of CSF is formed in the 3rd and 4th ventricles, and a negligible amount is produced in the vessels around the spinal column. As mentioned earlier, tiny finger-like projections in the SAS, called arachnoid villi, act as 1-way valves to absorb CSF into the dural sinuses to be carried out of the skull via the jugular veins. The arachnoid villi have the ability to open a lot or a little to shunt more or less CSF from the skull. The SAS around the spinal column has the ability to expand and accommodate increased volume if necessary, making this another great compensatory mechanism for decreasing overall cerebral volume. In addition, the SAS acts as the brains lymphatic system to carry dead cells and debris out of the skull and can be an accessory pathway for interstitial fluid to be slowly reabsorbed and drained from the skull. Unfortunately, the arachnoid villi may become clogged by infectious debris or blood and their ability to reabsorb CSF may be impaired or overwhelmed.

PATHOPHYSIOLOGY OF BRAIN EDEMA IN BRAIN TUMORS

Brain edema is a prominent feature of brain cancer and often contributes to neurologic dysfunction and impaired quality of life. Brain edema in brain tumors is the result of leakage of plasma into the parenchyma through dysfunctional cerebral capillaries. Vascular endothelial growth factor-induced dysfunction of tight junction proteins probably plays an important role in the formation of edema.

Clinical presentation :

Papilledema, occipital headache worsening in the morning, nausea and vomiting, abnormal eye movements, and impaired consciousness are the classic signs of raised intracranial pressure. Headache can be a prominent feature of patients with brain edema and is probably caused by traction or pressure on pain-sensitive structures such as dural coverings and blood vessels. In one large series, 60% of patients with brain tumors reported headache. The pain seems dependent on size and location of the tumor (infra- *vs* supratentorial), presence of midline shift, a prior history of headaches, and the amount of edema surrounding the tumor. Headache in patients with cancer is

an ominous sign: Intracranial metastases were found in more than 30% of cancer patients with headache as the presenting symptom. Headache duration of 10 weeks or less, emesis, and pain not of a tension type are significant clinical predictors for the presence of brain metastases in cancer patients. An important, although less frequently found, feature is papilledema. However, its absence would not exclude a brain tumor: Papilledema was absent in more than two thirds of patients with cerebellar metastases and headache.

In older patients with atrophic brains, the occurrence of brain edema would often not result in increased intracranial pressure, probably because of a surplus of intracranial space, and this may explain the more conspicuous absence of papilledema in the elderly. Vomiting is more common in children than in adults, and is more often associated with infratentorial lesions. Hemiparesis, dysphasia, cognitive decline, and other focal neurologic signs may either be the result of brain edema or of tumor growth. Thirty to 40% of patients with brain tumors present with focal neurologic deficits, and a similar percentage develops epilepsy.

Infratentorial lesions need special attention given the vulnerability of the brainstem. Under these conditions, a small amount of edema may result in severe symptoms of increased intracranial

pressure such as impaired consciousness, and emergency treatment is often necessary.

Pathology and pathophysiology :

During the last decade, pathophysiologic mechanisms of brain edema have been extensively studied. Brain edema can be defined as an expansion of brain volume resulting from an increase in water and sodium content.

Two major types of edema can be characterized: intra and extracellular edema.

Intracellular edema :

Increased intracellular water content results in cellular swelling. This type of edema is often the result of cytotoxic injury such as cerebral ischemia or trauma and is therefore called “cytotoxic edema.” In this type of edema, the primary targets are the ATP-dependent sodium pumps: Energy depletion-induced dysfunction of these pumps results in increased intracellular sodium levels and, as a consequence, results in the accumulation of intracellular water. Cytotoxic edema is probably not an important component of brain tumor edema, although it may play a role in situations when (micro)circulation is impeded (*eg,* after brain herniation).

Extracellular edema :

In the extracellular compartment, water can either be part of the cerebrospinal fluid or of the interstitial fluid. The production of interstitial fluid is probably driven by a pressure and osmotic gradient, is often called “bulk flow,” and it may have a role in transporting nutrients and metabolites. An increase in extracellular water leads to brain edema. This type of edema is mostly located in the white matter. Its properties, consisting of axons running parallel to one other and surrounded by an extracellular space with a low cell density, would contribute to a concentration of the edema within the white matter and may also serve as a conduit for transporting fluid.

The various types of extracellular edema are as follows:

Vasogenic edema is the most common type in brain tumors. As a result of increased brain capillary permeability and a pressure gradient from vascular to extracellular compartments, plasma leaks into the brain parenchyma and follows the pathways of bulk flow. This type of edema is described in more detail in the next section. Hydrocephalic edema is the result of the obstruction of cerebrospinal fluid flow. Edema is formed because of a hydrostatic pressure gradient between the ventricles and the brain parenchyma. Brain capillaries are not

affected, and restitution of the normal cerebrospinal fluid flow will therefore lead to clearance of hydrocephalic edema.

Osmotic edema is the result of an altered osmotic gradient between the plasma and the interstitial fluid. Severe osmotic edema can be seen after water intoxication, acute hyponatremia, or too rapid reduction of hyperosmolarity. Stasis, induced by tumor in venous drainage areas (*eg,* compression of an adjacent cortical vein by the tumor), with stasis at the site of the compression, results in peritumoral edema.

An excretory–secretory mechanism in meningiomas in which tumor-produced substances appear in the peritumoral tissue was postulated in the 1980s.

Based on electron microscopic studies, a close correlation was found between secretory activity and production of edema. Hydrodynamic processes, in which fluids originate from the tumor itself, may contribute to the formation of edema. It was recently shown that contrast agent effusion from the extracellular space of meningiomas into the interstitium of the peritumoral tissue was detectable 3 to 6hours after contrast administration.

Morphologic and molecular alterations in the blood–brain barrier :

The blood–brain barrier is a highly selective interface separating the brain from the blood. Its most important component is the capillary endothelial cell. In contrast to extracerebral capillaries, cerebral endothelial cells are nonfenestrated, lack intracellular clefts, contain low numbers of pinocytotic vesicles, have a high mitochondrial content, and are enclosed by astrocytic foot processes.

These endothelial cells are connected by tight junctions, which have both a high electric impedance and a low permeability to polar solutes, and they contribute to the selective barrier in this way. Opening of tight junctions probably plays a key role in the formation of vasogenic brain edema.

Edema accumulates around brain tumors at a rate of 14 to 78 ml/day. Absorptive mechanisms help to maintain equilibrium between edema formation and edema absorption. Edema is absorbed by transependymal flow into the ventricles and by absorption into microvessels.

The resulting excess of extracellular protein is removed by phagocytosis by astrocytes and microglia. The proteins occludin, claudins, and the junctional adhesion molecule are all part of the

molecular composition of tight junctions in the normal brain . These transmembrane proteins bind intracellular proteins such as ZO-1 and ZO-2, and this binding results in the coupling of tight junctions to the cytoskeleton of 594 Brain and nervous system endothelial cells. One has suggested that a decreased expression or function of these tight junction proteins leads to opening of the tight junction and to the formation of edema. Several studies support this hypothesis. For example, microvessels in glioblastoma multiforme express only low levels of claudin-1, and high-grade gliomas (grades III and IV) do not express functional occludin. A key mediator in these mechanisms is vascular endothelial growth factor (VEGF).

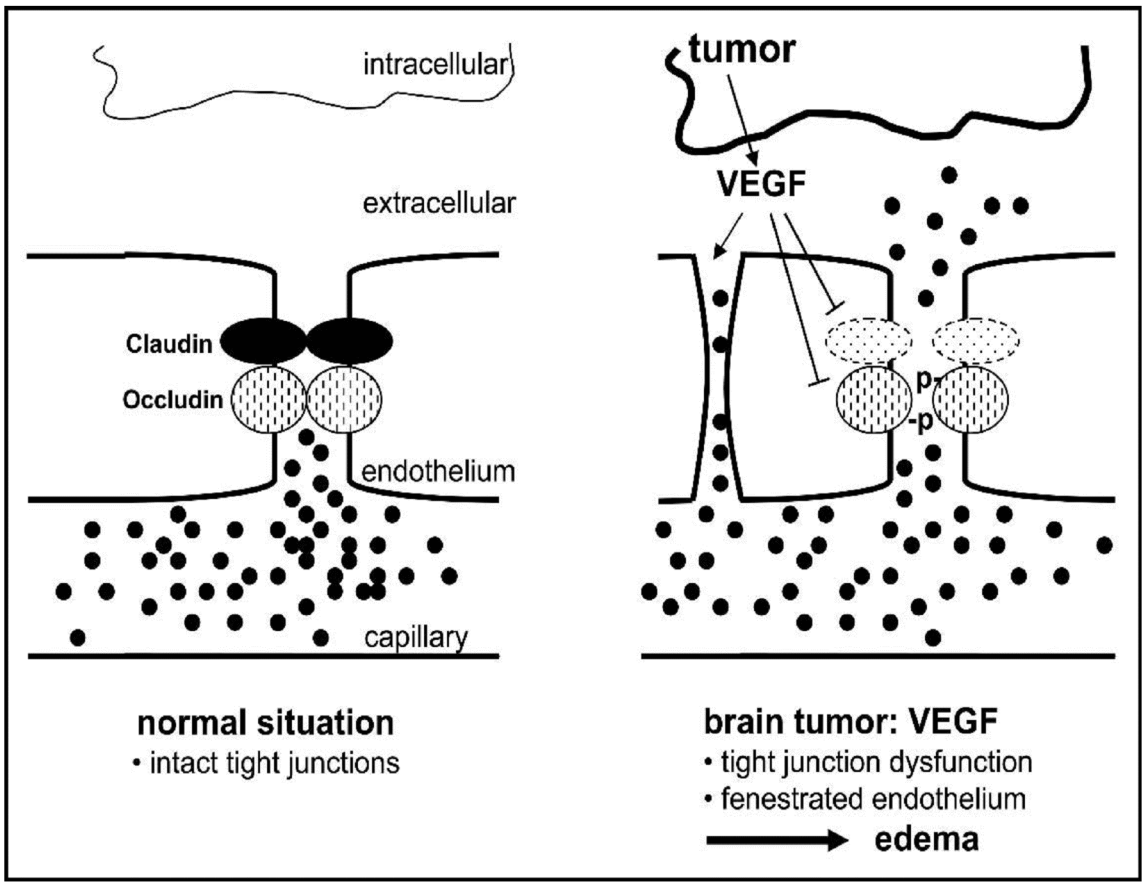
Vascular endothelial growth factor

VEGF was originally described as vascular permeability factor and it functions as a regulator of angiogenesis and vascular permeability. VEGF binds to endothelial cells via interaction with the high-affinity tyrosine kinase receptors FLT-1 (VEGFR-1) and FLK-1/KDR (VEGFR2).

These receptors are expressed predominantly on endothelial cells. VEGF has a very strong vascular permeability activity and is a thousand times more potent than histamine, and probably has direct effects on the endothelial tight junction (which is described later). Besides, VEGF induces edema formation via the synthesis and release of nitric oxide, an activator of cyclic GMP-dependent pathways. VEGF may impair the function of occludin: VEGF phosphorylates occludin, with the opening of tight junctions as a consequence. Others report that VEGF induces fenestration of the endothelium and enhances capillary permeability in this way. The role and expression of VEGF in meningiomas and gliomas is discussed in the next section. VEGF-mediated vasogenic edema is presented in Figure 1.

Mechanism Of VEGF-Mediated Vasogenic Edema Formation

(Figure 1)



Alternative hypotheses on the formation and regulation of brain edema have been generated after the discovery of the aquaporin family. In the brain, aquaporin-4 is expressed in endothelial astrocytic foot processes. Aquaporin- 4 is highly upregulated in high-grade gliomas. Whether this upregulation results in increased edema formation or in enhanced clearance of edema is still unclear.

OTHER MEDIATORS OF EDEMA :

Apart from VEGF, other vasoactive substances released by the tumor itself or by the injured peritumoral tissue may contribute to the formation of brain edema. Arachidonic acid metabolites may be important in this respect: Elevated levels of leukotriene C4 (produced via the lipoxygenase pathway) are found in glioblastoma multiforme, as well as in the surrounding edematous tissue.

More important, the concentration of leukotriene C4 correlates significantly with the amount of peritumoral edema. Another interesting aspect is the observation that the degree of peritumoral macrophage infiltration is associated with the amount of edema. This has prompted the suggestion that secretory products of macrophages would contribute to the formation of edema.

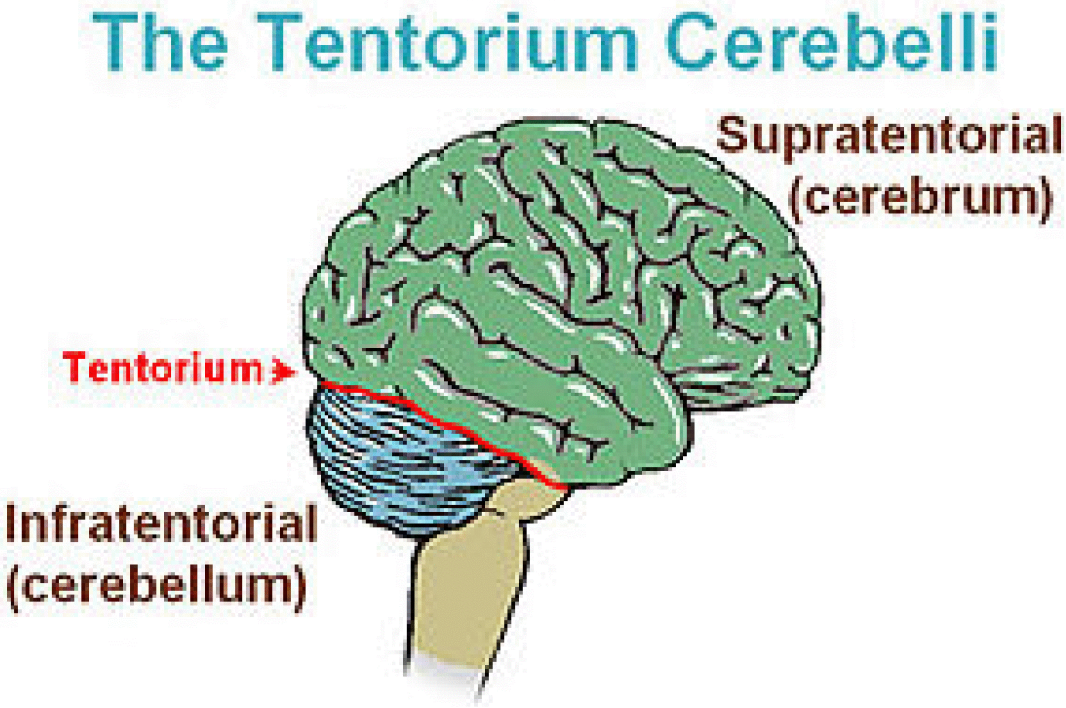
The list of other potential vasogenic substances that may promote the development of brain edema is long, including serotonin, thromboxanes, and platelet-activating factor.

Neurological Compensatory Mechanisms :

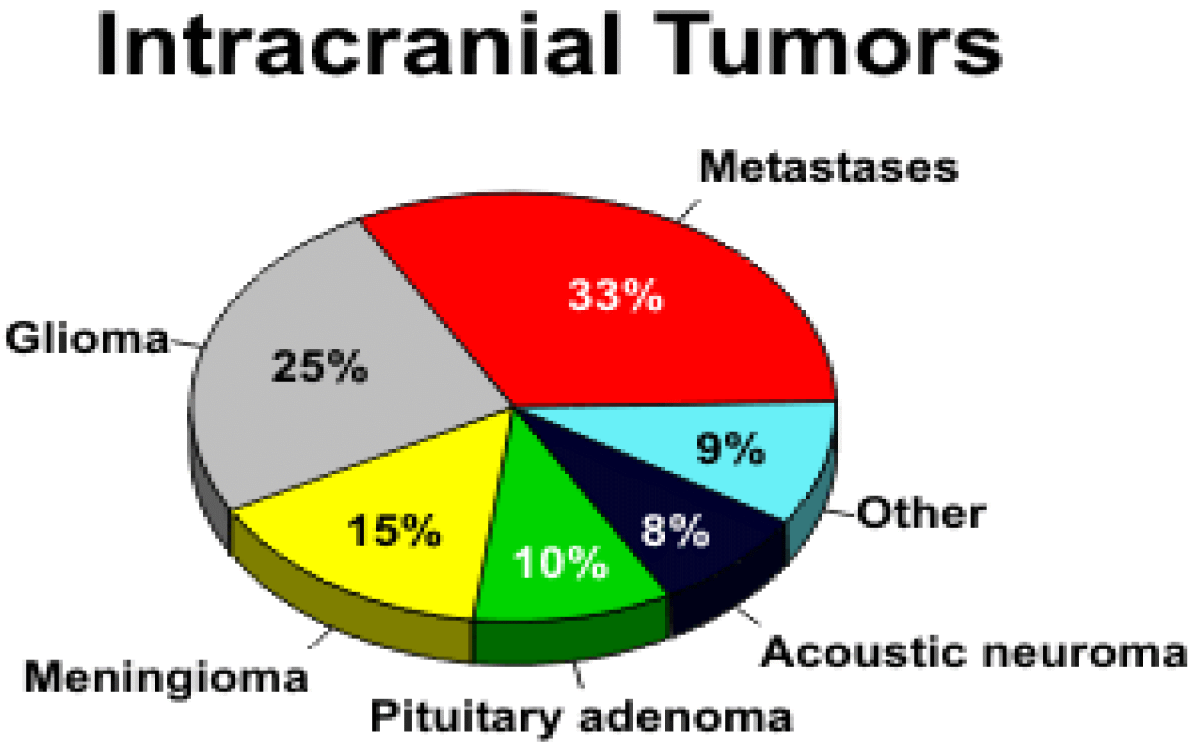
1. Decrease production rate of CSF, secondary to decreased cerebral blood volume.
2. Shunt more CSF out of skull into spinal SAS.
3. Increase rate of reabsorbtion of CSF into duaral sinuses by opening of arachnoid villi.
4. Decrease cerebral blood volume via autoregulation and vasoconstriction.
5. Spontaneous hyperventilation to vasoconstrict cerebral vessels and limit cerebral blood and blood have an intimate and dynamic relationship with each other.

Under normal circumstances volume of the brain has a large capacity for self-protection and for compensating in the initial stages of an injury. This can be accomplished through autoregulation, augmenting or restricting blood flow, the shunting of CSF and venous blood from the skull, and decreasing the production of CSF. After compensatory mechanisms have been exhausted, intracranial pressure will rise depriving vulnerable tissue the oxygen and glucose it needs

TYPES OF SUPRATENTORIAL BRAIN TUMOURS

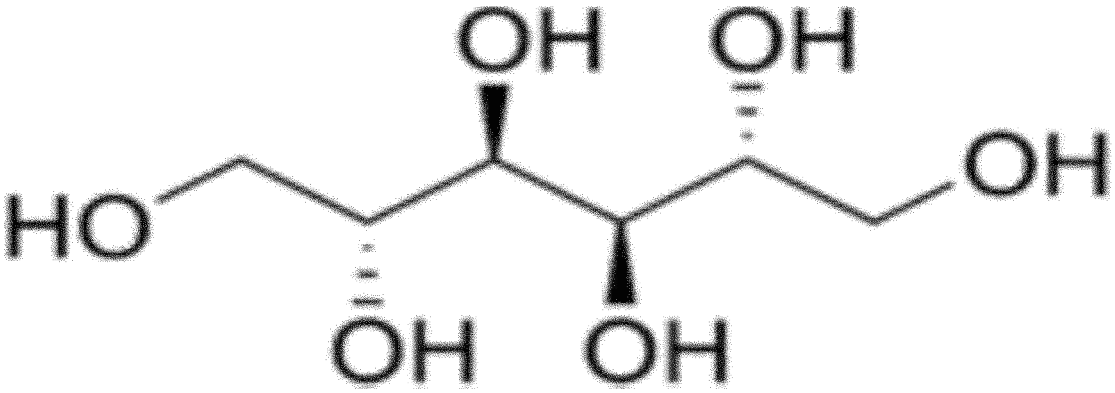


1) Tumours arising from brain above the tentorium of the brain are called supratentorial brain tumours.
2) This tumours are completely packed by surrounding structures skull above and side and tentorium below.
3) Paves way for easy rise of intra cranial tension and stretched duramater due to continuous growth of supratentorial tumours.

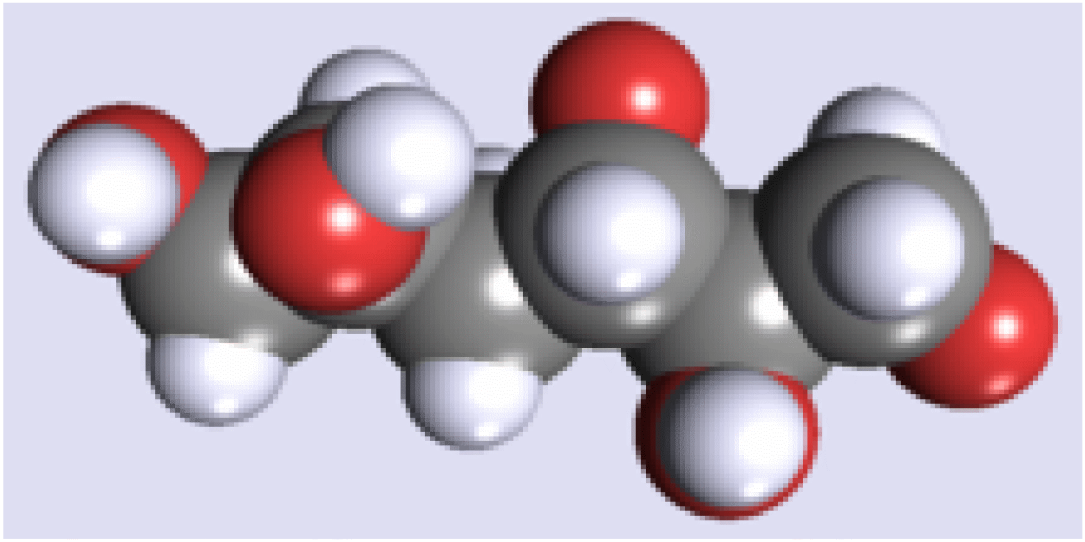


1. Most commonly reported primary superatentorial tumour is glioma.
2. Second most commonly reported tumour is meningioma. metastatic tumour is most common tumour of all cerebral tumours.

PHYSICAL CHEMISTRY AND PHARMACOLOGY OF MANNITOL



d- MANNITOL



MANNITOL :

IUPAC NAME	2R,3R,4R,5R –HEXOL
FORMULA	C6H14O6
MOLECULAR MASS	182.172

PHARMACOKINETIC DATA :

METABOLISM - liver

EXCRETION - kidney 90%

HALF LIFE - 100 minutes

MANNITOL : (also referred to as mannite or manna sugar)

D-Mannitol (here: mannitol) is a naturally occurring sugar alcohol with six carbon atoms. It is only half as sweet as sucrose. However, mannitol and other sugar alcohols exhibit reduced caloric values compared to the respective value of most Sugars, which make them applicable as sweeteners in so-called “light” foods. Moreover, sugar alcohols are metabolized independently of insulin and are thus also applicable in diabetic food products. Besides applications in the food industry, mannitol is also used in the pharmaceutical industry.

In medicine, mannitol is used to decrease cellular edema (excessive accumulation of fluid) and increases the urinary output.

Sugar alcohols, also known as polyols, are the hydrogenated form of sugars. Hydrogenation reactions involve the addition of hydrogen atoms. In the case of Monosaccharide hydrogenation, free hydrogen atoms attack the carbonyl group, resulting in the breakdown of the C=O double bond. Monosaccharides are polyhydroxy ketones and aldehydes and thus, the location of the carbonyl group varies among the different sugars.

In D-fructose, also known as fruit sugar, the Second carbon atom forms the carbonyl group and when hydrogenated, D-mannitol And D-sorbitol are formed (Figure 1). Hence, the two hydrogen atoms

added in the reaction are bound to carbon number two and to the oxygen atom of the same carbon atom. Other common sugar alcohols derived from monosaccharides are e.g. Xylitol (from xylose) and Ribitol (from ribose). Sorbitol is usually derived by hydrogenation of glucose.

NATURAL OCCURRENCE OF MANNITOL

D-Mannitol is a naturally occurring sugar alcohol found in animals and plants. It is present in small quantities in most fruits and vegetables (Ikawa et al., 1972). Typically, it can be found in such plants as pumpkins, celery, onions, grasses, olives, Mistletoe, and lichens. Mannitol is also found in manna, the dried exudate of the Manna ash tree (Fraxinus ornus) (Schwarz, 1994). Manna is obtained by heating the bark of the tree and it can contain up to 50% mannitol. Hence, manna has been a commercial source of mannitol in Sicily, Italy (Soetaert et al., 1999).

Marine algae, especially brown algae, are also rich in mannitol (10-20% depending on the time of harvest) (Schwarz, 1994). Furthermore, mannitol is commonly found in the mycelium of various fungi and it is present in fresh mushrooms at about 1%.

GENERAL PROPERTIES OF MANNITOL

The properties of mannitol (mannite, D-mannohexane-1,2,3,4,5,6-hexaol, mannitolum, Mannitolo, or manna sugar) are fairly similar to those of its stereoisomer, Sorbitol. However, the solubility of mannitol in water is significantly lower than that of sorbitol and most of the other sugar alcohols. At 14°C the solubility of mannitol. In water

is only approximately 13% (w/v) (Perry et al., 1997). At 25°C the solubility of mannitol in water is approximately 18% (w/v) (Soetaert et al., 1999). Mannitol is sparingly soluble in organic solvents, like ethanol and glycerol, and practically insoluble in ether, ketones, and hydrocarbons (Schwarz, 1994). The relative sweetness (to sucrose) varies among different sugar alcohols. The relative sweetness of xylitol is 100%, whereas the relative sweetness of mannitol is only 40-50% (Schiweck et al., 1994; Anon., 2001a). Mannitol forms white orthorhombic needles and the crystals have a melting point of 165-168°C (Schwarz, 1994). Owing to the high positive heat (or enthalpy) of solution in water, 120.9 Kj/kg (Schiweck et al., 1994; Lawson, 1997), a cooling sensation occurs when mannitol crystals dissolve in the mouth. This effect is commercially used in e.g. Chewing gums, but is less pronounced than that observed with xylitol (153.1 kj/kg) (Schiweck et al., 1994; Lawson, 1997). Crystalline mannitol exhibits a very low hygroscopicity (it does not add moisture or contribute to moisture pick-up). Moreover, it is also chemically inert. These properties make mannitol very useful in Production of tablets and granulated powders.

CHEMISTRY OF MANNITOL :

It is a white, crystalline solid with the chemical formula $C_6H_8(OH)_6$. It was originally isolated from the secretions of the flowering ash and called manna after its resemblance to the biblical food. In plants, it is used to induce osmotic stress. It has several industrial uses, but is mainly used to produce tablets of medicine. Its fetal safety is "C" in Briggs' reference guide to fetal and neonatal risk. Mannitol is classified as a sugar alcohol; that is, it is derived from a sugar (mannose) by reduction. Other sugar alcohols include xylitol and sorbitol. Mannitol and sorbitol are isomers, the only difference being the orientation of the hydroxyl group on carbon 2.

Mannitol is used clinically in osmotherapy to reduce acutely raised intracranial pressure until more definitive treatment can be applied, e.g., after head trauma. It is also used to treat patients with oliguric renal failure. It is administered intravenously, and is filtered by the glomeruli of the kidney, but is incapable of being reabsorbed from the renal tubule, resulting in decreased water and sodium reabsorption via its osmotic effect. Consequently, mannitol increases water and Na^+ excretion, thereby decreasing extracellular fluid volume.

Mannitol can also be used as a facilitating agent for the transportation of pharmaceuticals directly into the brain. The arteries of the blood–brain barrier are much more selective than normal arteries. Normally, molecules can diffuse into tissues through gaps between the endothelial cells of the blood vessels. However, what enters the brain must be much more rigorously controlled. The endothelial cells of the blood–brain barrier are connected by tight junctions, and simple diffusion through them is impossible. Rather, active transport is necessary, requiring energy, and only transporting molecules that the arterial endothelial cells have receptor signals for. Mannitol is capable of opening this barrier by temporarily shrinking the endothelial cells, simultaneously stretching the tight junctions between them. An intracarotid injection of high molarity mannitol (1.4–1.6M), causes the contents of the artery to be hyperosmotic to the cell. Water leaves the cell and enters the artery in order to recreate an osmotic equilibrium. This loss of water causes the cells to shrivel and shrink, stretching the tight junctions between the cells. The newly formed gap reaches its peak width five minutes after mannitol injection, and stays widely open for thirty minutes. During this time span, drugs injected into the artery can easily diffuse though the gaps between cells directly into the brain. This makes mannitol indispensable for delivering various drugs

directly to the brain (e.g., in the treatment of Alzheimer's disease, or in chemotherapy for brain tumors.)

Mannitol is commonly used in the circuit prime of a heart lung machine during cardiopulmonary bypass. The presence of mannitol preserves renal function during the times of low blood flow and pressure, while the patient is on bypass. The solution prevents the swelling of endothelial cells in the kidney, which may have otherwise reduced blood flow to this area and resulted in cell damage.

Mannitol is also the basis of Bronchitol which was developed by the Australian pharmaceutical company. Pharmaxis as a treatment for cystic fibrosis and bronchiectasis. The mannitol is orally inhaled as a dry powder through what is known as an osmohaler and osmotically draws water into the lungs to thin the thick, sticky mucus characteristic of cystic fibrosis. This is intended to make it easier for the sufferer to cough the mucus up during physiotherapy. The critical characteristic of the mannitol is its particle size distribution.

Mannitol is also the first drug of choice for the treatment of acute glaucoma in veterinary medicine. It is administered as a 20% solution IV. It dehydrates the vitreous humor and, thus, lowers the

intraocular pressure. However, it requires an intact blood-ocular barrier to work.

Mannitol can also be used to temporarily encapsulate a sharp object (such as a helix on a lead for an artificial pacemaker) while it is passed through the venous system. Because the mannitol dissolves readily in blood, the sharp point will become exposed at its destination.

Mannitol may be administered in cases of severe ciguatera poisoning. severe ciguatoxin, or "tropical fish poisoning" can produce stroke-like symptoms.

Mannitol is the primary ingredient of mannitol salt agar, a bacterial growth medium, and is used in others.

In oral doses larger than 20g, mannitol acts as an osmotic laxative, and is sometimes sold as a laxative for children. The use of mannitol, when inhaled, as a bronchial irritant as an alternative method of diagnosis of exercise induced asthma has been proposed. A 2013 systematic review concluded there is insufficient evidence to support its use for this purpose at this time.

Food :

Mannitol increases blood glucose to a lesser extent than sucrose (thus having a relatively low glycemic index) and is

therefore used as a sweetener for people with diabetes, and in chewing gums. Although mannitol has a higher heat of solution than most sugar alcohols, its comparatively low solubility reduces the cooling effect usually found in mint candies and gums. However, when mannitol is completely dissolved in a product, it induces a strong cooling effect. Also, it has a very low hygroscopicity- it does not pick up water from the air until the humidity level is 98%. This makes mannitol very useful as a coating for hard candies, dried fruits, and chewing gums, and it is often included as an ingredient in candies and chewing gum. The pleasant taste and mouth feel of mannitol also makes it a popular excipient for chewable tablets.

Analytical chemistry

Mannitol can be used to form a complex with boric acid. This increases the acid strength of the boric acid permitting better precision in volumetric analysis of this acid.

Illicit drugs :

Mannitol is sometimes used as an adulterant or cutting agent for heroin, methamphetamines, cocaine, or other illicit drugs. In popular culture, when it is used in this manner, it is often referred to as baby laxative.

Industrial synthesis :

Mannitol is commonly produced via the hydrogenation of fructose, which is formed from either starch or sucrose (common table sugar). Although starch is a cheaper source than sucrose, the transformation of starch is much more complicated. Eventually, it yields a syrup containing about 42% fructose, 52% dextrose and 6% maltose. Sucrose is simply hydrolyzed into an invert sugar syrup, which contains about 50% fructose. In both cases, the syrups are chromatographically purified to contain 90–95% fructose. The fructose is then hydrogenated over a nickel catalyst into mixture of isomers sorbitol and mannitol. Yield is typically 50% : 50%, although slightly alkaline reaction conditions can slightly increase mannitol yields.

Biosynthesis :

Mannitol is one of the most abundant energy and carbon storage molecules in nature, produced by a plethora of organisms, including bacteria, yeasts, fungi, algae, lichens, and many plants. Fermentation by microorganisms is an alternative to the traditional industrial synthesis. A fructose to mannitol metabolic pathway, known as the mannitol cycle in fungi, has been discovered in a type of red

algae (Caloglossa leprieurii), and it is highly possible that other microorganisms employ similar such pathways. A class of lactic acidbacteria, labeled heterofermentive because of their multiple fermentation pathways, convert either three fructose molecules or two fructose and one glucose molecule into two mannitol molecules, and one molecule each of lacticacid, aceticacid, and carbon dioxide. Further research is being conducted, studying ways to engineer even more efficient mannitol pathways in lactic acid bacteria, as well as the use of other microorganisms such as yeast and E.coli in mannitol production. When food grade strains of any of the aforementioned microorganisms are used, the mannitol and the organism itself are directly applicable to food products, avoiding the need for careful separation of microorganism and mannitol crystals. Although this is a promising method, steps are needed to scale it up to industrially needed quantities.

Natural product extraction :

Since mannitol is found in a wide variety of natural products, including almost all plants, it can be directly extracted from natural products, rather than chemical or biological syntheses. In fact, in China, isolation from seaweed is the most common form of mannitol

production. Mannitol concentrations of plant exudates can range from 20% in seaweeds to 90% in the plane tree. It is a constituent of saw palmetto (Serenoa). Traditionally, mannitol is extracted by the Soxhlet extraction, utilizing ethanol, water, and methanol to steam and then hydrolyze the crude material. The mannitol is then recrystallized from the extract, generally resulting in yields of about 18% of the original natural product. Another up and coming method of extraction is by using supercritical and subcritical fluids. These fluids are at such a stage that there is no difference between the liquid and gas stages, and are therefore more diffusive than normal fluids. This is considered to make them much more effective mass transfer agents than normal liquids. The super-/sub-critical fluid is pumped through the natural product, and the mostly mannitol product is easily separated from the solvent and minute amount of byproduct. Supercritical carbon dioxide extraction of olive leaves has been shown to require less solvent per measure of leaf than a traditional extraction- 141.7 g (5.00 oz) CO_2 versus 194.4 g (6.86 oz) ethanol per 1 g (0.035 oz) olive leaf. Heated, pressurized, subcritical water is even cheaper, and is shown to have dramatically greater results than traditional extraction. It requires only 4.01 g (0.141 oz) water per 1 g (0.035 oz) of olive leaf, and gives a yield of 76.75% mannitol. Both

super- and sub-critical extractions are cheaper, faster, purer, and more environmentally friendly than the traditional extraction. However, the required high operating temperatures and pressures are causes for hesitancy in the industrial use of this technique.

REVIEW OF LITERATURE

Osmotherapy can be defined broadly as the use of osmotically active solutions to reduce the volume of the intracranial contents. The first description of the principles of osmotherapy as applied to the central nervous system (CNS) is often attributed to Weed and McKibben in 1919 their interpretation has formed the foundation of the concept of "osmotherapy" as it may be applied to treatment of space-occupying intracranial pathology.

1. In 1927, Fremont-Smith and Forbes formalized the intravenous delivery of osmotic agents for clinical practice, first making the use of concentrated urea.
2. Hughes et al were the first to demonstrate that concentrated solutions of human plasma proteins could effectively reduce raised intracranial pressure (ICP). However, concerns about allergic reactions and the cost of preparation of concentrated human plasma limited early interest in "oncotic therapy."
3. Wise and Chater clearly demonstrated that the carbohydrate mannitol was a more practically useful agent. Unlike urea, mannitol was easy to prepare, chemically stable in solution, and

did not produce vein irritation when infused, among other desirable properties that are discussed later. Intravenous mannitol infusions subsequently became a central modality in controlling of intracranial hypertension.

4. In the 1970s, the work of Little, Sundt, and Crowell and Olsson identified the potentially beneficial rheologic effects of mannitol and other osmotic agents in the management of cerebral ischemia.
5. More recently, several investigators, most notably Rosner and Coley and Muizelaar et al, have challenged the nostrum that osmotherapy is based on direct osmotic action and "shrinkage" of the brain parenchyma. Alternative theories that emphasize dynamic changes in cerebral blood volume (CBV) and CSF circulation have been put forth. In general, these theories reflect a more differentiated view of the volume dynamics of the intracranial space.
6. Rosner has opined that in general, the ideal agent for use in osmotherapy is a rapidly excreted diuretic that establishes strong trans-endothelial osmotic gradients. Mannitol comes as close to this ideal as any agent currently available. An additional advantage of mannitol which is typically administered as a rapid

intravenous infusion; is the potentially beneficial hemodynamic effects resulting from the bolus itself.

7. As per Cote et al the effect of a mannitol bolus on systemic arterial pressure is variable. A slight increase in pulse pressure and mean arterial blood pressure is most commonly observed, but transient decreases in blood pressure secondary to decreases in systemic vascular resistance are not uncommon and have been described definitively in the literature.
8. Findlay et al have tried to explain the mechanisms of vasodilatory effects of mannitol. As per their opinion the acute vasodilatory effect of mannitol is not well understood and has been related to mechanisms as diverse as decreases in plasma pH, release of atrial natriuretic factor, histamine release from basophils, and direct impairment of the contractile properties of vascular smooth muscle.
9. Barry et al have looked at systematically administered mannitol boluses to patients with reduced left or right ventricular function. Presumably because of the rapid clearance of mannitol from the plasma, signs and symptoms of congestive heart failure were not observed in this series. According to them precaution must be taken in the case of patients with impaired renal clearance. If

osmotherapy is used at all in this population, the dose and dosing interval should be decreased and increased, respectively. In addition, monitoring of pertinent hemodynamic variables that may guide the course of therapy should be considered.

10. Richard et al have emphasized that an important practical point being the ratio of the volume of fluid diuresed to the volume of mannitol administered, which may be appreciably high, approaching five for a 25% solution of mannitol (the approximate ratio of the osmolality of mannitol to normal plasma osmolality). According to them, this fact readily explains the extent to which marked dehydration of the body can result from administration of osmotic diuretics. Hyperosmolar dehydration can be insidious. Unlike hemorrhage or relatively isotonic volume losses, which cause early clinical signs of impending hemodynamic instability, gradual hypertonic dehydration occurs in the presence of mounting osmotic and oncotic gradients favouring movement of fluid from the tissues into the vascular space. These forces tend to preserve circulating volume. Clinical signs of hemodynamic compromise therefore may not develop until quite late, when extravascular dehydration is severe.

11. Nikki et al et al have shown the hemodynamic changes in response to a single dose of mannitol using non invasive cardiac output monitor, in patients undergoing craniotomy. They have measured blood pressure by non invasive means and cardiac output by bioimpedance plethysmography. They have shown that all post mannitol systolic blood pressure values were significantly lower than pre mannitol values, whereas stroke volume increased significantly for 15 minutes after the infusion of mannitol, but at 45 minutes it was significantly lower than that from 1 to 30 minutes. Cardiac index also showed similar changes. The rate of urine output was higher during first 10 minutes than during rest of the study period.
12. Alfred and colleagues have shown that although osmotic agents are among the most fundamental tools to control ICP, prospective data to establish clear guidelines on their use are lacking.
13. Knapp has stated that intravenous bolus administration of mannitol lowers the ICP in 1 to 5 minutes; with a peak effect at 20 to 60 minutes. The effect of mannitol on ICP lasts 1.5 to 6 hours, depending on the clinical condition.

14. Muizelaar et al have shown that because of mannitol having rheologic and osmotic effects, infusion of mannitol is immediately followed by an expansion of plasma volume and a reduction in hematocrit and blood viscosity, which may increase CBF. The osmotic effect of mannitol increases serum tonicity and draws edema fluid from cerebral parenchyma. This process takes 15 to 30 minutes, until gradients are established. The effect of mannitol on intraoperative brain relaxation has been increasingly studied in recent years.
15. In 2007, Rozet et al. compared the effects of mannitol and hypertonic saline on intraoperative brain relaxation in 40 patients undergoing elective craniotomy and found a similar effect in both treatment groups. However, the intracerebral pathology of the patients in this study varied widely, and only six of the ten patients with supratentorial brain tumors received mannitol. Additionally, the preoperative peritumoral edema and intracranial pressure were not recorded, and only a single dose of mannitol (1 g/kg) was administered.
16. Wu et al. compared the effects of 160 ml of 3% hypertonic saline and 150 ml of 20% mannitol on brain relaxation. Their study suggested that 3% hypertonic saline provided better

relaxation; however, the lengths of hospital and intensive care unit stays did not significantly differ. The dose of mannitol administered in the study was not adjusted according to the preoperative intracranial pressure, the intracranial mass occupying effect, or the body weight of the patient. Furthermore, the dose of mannitol was lower than the commonly used clinical dose. Therefore, this study is of little use as a clinical guide.

17. Rozet et al. observed the effect of a single mannitol dose on brain relaxation in patients with widely varying intracerebral pathologies, including supratentorial tumor.

18. Quentin et al. examined the effects of two doses (0.7 and 1.5 g/kg) of mannitol on brain relaxation in tumor patients, neither of which was the routine clinical dose (1 g/kg); additionally, they did not consider the effect of preoperative intracranial mass. However, these studies indicated that the effect of mannitol on brain relaxation was dose-dependent. The current proposal is a prospective randomized controlled study that aims to examine the effects of three doses of mannitol on brain relaxation in patients with preoperative midline shift.

19. The above series of randomized control trials aimed to assess the effect of mannitol on brain edema and relaxation; however, there

were limitations associated with their conclusions. First, the studies did not describe preoperative factors that may affect brain relaxation, such as the size and histological type of the tumor, peritumoral edema, the position of the head and body, body temperature, and arterial carbon dioxide partial pressure. Second, the studies did not indicate whether high-risk patients with increased brain pressure were included. Finally, these studies lacked data comparing the clinical side effects and patient outcomes following the infusion of mannitol.

20. A randomized controlled trial of intraoperative intravenous mannitol in patients undergoing supratentorial tumor surgery will be conducted to examine this hypothesis.

MATERIALS AND METHODS

DESIGN OF STUDY:

A Prospective randomized double blinded study

COLLABORATING DEPARTMENT:

Neurosurgery

STUDY POPULATION :

After getting ethical committee approval and informed consent 48 patients of both sexes (male and female) who underwent elective craniotomy for supratentorial tumour surgeries under general anaesthesia at Government Rajaji Hospital, Madurai were taken up for study. 48 patients were divided into three groups as group-A group-B and group-C with 16 in each group. Each group were armed as follows.

ARMS	ASSIGNED INTERVENTIONS
GROUP A: I. 20% mannitol 0.5gm/kg II. Study subjects will be randomized to receive an infusion of 20% mannitol 0.5gm/kg over 3o minutes after induction.	I. Drug: mannitol II. Variation of mannitol dose.
GROUP B: I. 20% mannitol 1.0gm/kg II. Study subjects will be randomized to receive an infusion of 20% mannitol 1.0gm/kg over 3o minutes after induction.	I. Drug: mannitol II. Variation of mannitol dose.
GROUP C: I. 20% mannitol 1.5gm/kg II. Study subjects will be randomized to receive an infusion of 20% mannitol 1.5gm/kg over 3o minutes after induction.	I. Drug: mannitol II. Variation of mannitol dose.

INCLUSION CRITERIA :

1. Patients who are undergoing an elective craniotomy for supratentorial tumors under GA.
2. 18-60 Yrs.
3. Male /Female.
4. ASA 1 – 3.

EXCLUSION CRITERIA :

1. Pregnancy .
2. Congestive Heart Failure.
3. Chronic Renal Failure.
4. Recent use (< 24 hrs before surgery) of mannitol or other hypertonic solution.

PROBABILITY SAMPLING :

48 lots were randomized (16 in each group) from the people who were willing to take part in the study. All the patients stand an equal chance of getting into any group. All the patients were aware of the study and informed consent was obtained .

MATERIALS :

1. 20 % Mannitol

MONITORS USED :

1. Blood pressure monitor
2. End tidal carbon di oxide monitor
3. Multipara monitor
4. Temperature monitor
5. ABG analyser

METHODOLOGY

In the preoperative waiting room detailed history and physical examination was done. Basic investigations were collected. Baseline data like pulse rate, blood pressure, mean arterial pressure, spo2, temperature, serum electrolytes, preoperative arterial blood gases were recorded. Group A, Group B and Group C were explained about the procedures and follow up pattern. A standardized anaesthetic technique was used.

All patients were premedicated with inj.glycopyrolate 0.2mg intramuscularly 45 minutes before surgery. Monitors were connected. Intravenous canula secured and connected to i.v. fluids. Another Intravenous canula secured for infusion of 20% mannitol. Patients were preoxygenated with 100% O2 for 3 minutes. Patients were induced with injection fentanyl 2 micrograms per kilogram of body weight, thiopentone 5 milligram per kilogram of body weight, injection succinyl choline was avoided in my study, because to avoid rise in intracranial pressure. For that injection vecronium of 0.08 miligram per kilogram of body weight was used. To blunt the intubation response injection 2% lignocaine of 1.5mg/kilogram was given intravenously. Patients were intubated with 7 size / 7.5 size endotracheal tube for female and 8 size/ 8.5 size endotracheal tube for male was used.

Bilateral air entry checked and connected to closed circuit. Patient is maintained with N20:O2 in 2:2 with injection fentanyl 1 micrograms per kilogram of body weight every 45 minutes and injection vecronium in titrated doses. ETCO2 was maintained in 25-30 mmHg range throughout the procedure. Haemodyanamic variables like blood pressure, mean arterial pressure, pulse rate and spo2 were measured immediately prior to the infusion of mannitol, at 30 and 60 minutes after the administration of mannitol. Similarly urine out put, perioperative fluid balance, blood loss and Laboratory data's like arterial blood PH, electrolytes were measured immediately prior to the infusion of mannitol, at 30 and 60 minutes after the administration of mannitol. Datas were recorded according to the time frame. At the time opening duramater, brain relaxation was assessed by a neuro surgeon on scale from 1 to 4 which was given as follows.

At the end of surgery, after adequate attempts of respiration patients were reversed with injection glycopyrolate of 10 micrograms per kilogram of body weight and injection neostigmine of 40 micrograms per kilogram of body weight . Adequate suctioning done. To blunt the extubation response injection 2% lignocaine of 1.5mg/ kilogram was given. Patients were then extubated after gaining adequate muscle power.

PARAMETERS MONITORED INTRAOPERATIVELY

PRIMARY OUTCOME MEASURES :

- Brain relaxation at the opening of the duramater assessed by a neuro surgeon on scale (ROZET QUENTIN scale) from 1 to 4.
- Scale 1: perfectly relaxed (shrunken dura with prominent veins)
- Scale 2: satisfactorily relaxed (only prominent veins)
- Scale 3: firm brain
- Scale 4: bulging brain
- Time frame : at the opening of the dura mater.

SECONDARY OUTCOME MEASURES :

- **Haemodynamic variables: -**

  Mean arterial blood pressure, Heart rate, Blood pressure, SPO2.

  Time frame - immediately prior to the infusion of mannitol, at 30 and 60minutes after the administration of mannitol.

- **Urine output :**

  Time frame - immediately prior to the infusion of mannitol,

  at 30 and 60 minutes after the administration of

  mannitol.

- **Perioperative fluid balance and blood loss :**

  Time frame - immediately prior to the infusion of mannitol

  at 30 and 60 minutes after the administration of

  mannitol.

- **Laboratory data:**

  Blood PH, electrolytes.

  Time frame - immediately prior to the infusion of mannitol,

  at 30 and 60minutes after the administration of

  mannitol.

DATA ANALYSIS

The observations were recorded for three groups as shown in the master chart.

STATISTICAL TOOL APPLIED :

The information collected regarding all the selected cases were recorded in a master chart. Data analysis was done with the help of computer using epidemiological information package (EPI 2010) developed by centre for disease control, Atlanta.

- Range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated using computer based software(SPSS statistical tool).
- Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables.
- Yate's chi square test for qualitative variables.
- A 'p' value less than 0.05 is taken to denote significant relationship.

OBSERVATION AND RESULTS

TABLE 1:

BRAIN RELAXATION SCORE :

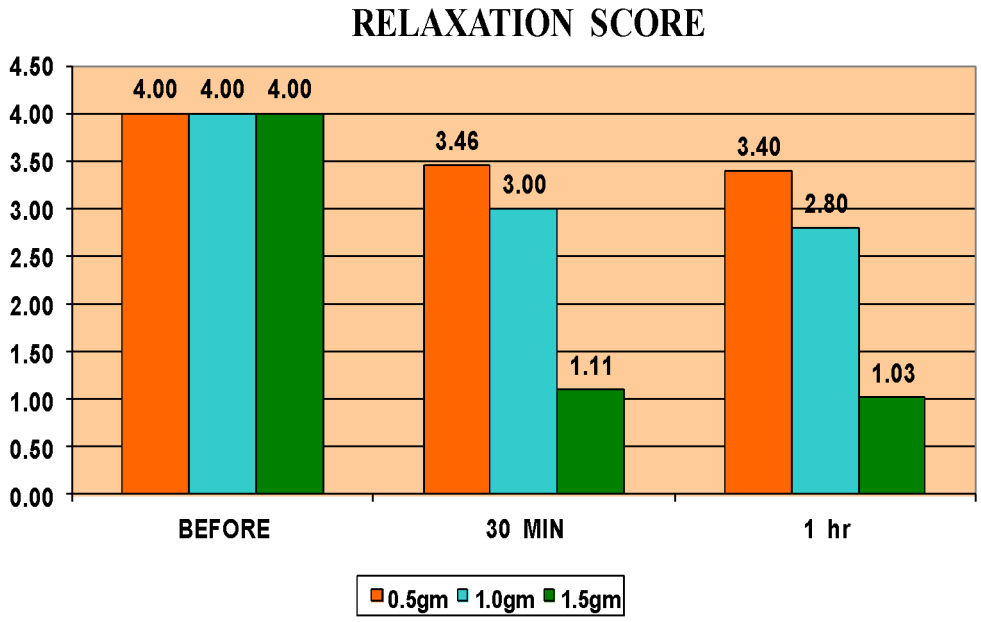
20% MANNITOL	BEFORE	30 MIN	1 HR
0.5GM	4.00	3.46	3.40
1.0GM	4.00	3.00	2.80
1.5GM	4.00	1.11	1.03
P' VALUE	1.00 NS	< 0.001 SIG	< 0.001 SIG

A. In this brain relaxation score P value is less than 0.005

B. There is significant change in brain relaxation score with increasing dose of mannitol .

CHART 1 :

BRAIN RELAXATION SCORE :



A. There is significant change in brain relaxation score with increasing dose of mannitol .

B. Relaxation is perfect with increasing dose of mannitol.

TABLE 2 :

MEAN ARTERIAL BLOOD PRESSURE :

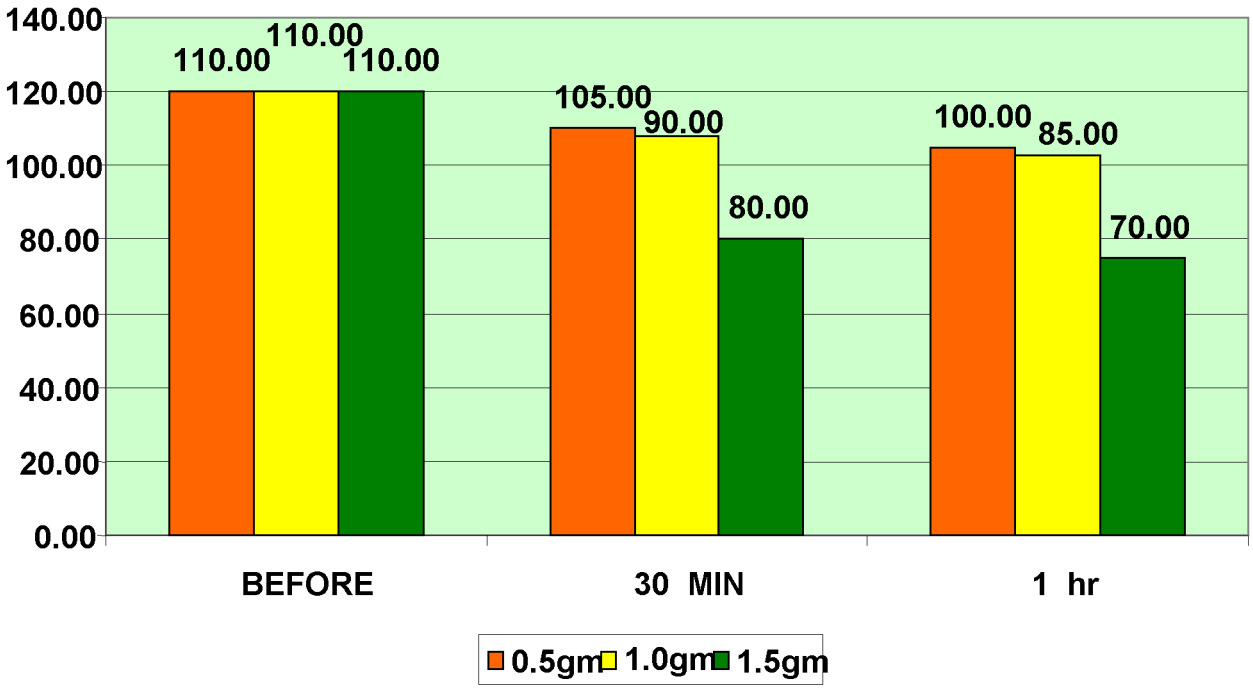
20% MANNITOL	BEFORE	30 MIN	1 HR
0.5gm	110.00	105.00	100.00
1.0gm	110.00	90.00	85.00
1.5gm	110.00	80.00	70.00
p' value	1.00 NS	< 0.001 Sig	< 0.001 Sig

A. In this mean arterial blood pressure, P value is less than 0.005

B. There is significant change in mean arterial blood pressure with increasing dose of mannitol .

CHART 2 :

MEAN ARTERIAL BLOOD PRESSURE :



A. There is significant change in mean arterial blood pressure with increasing dose of mannitol .

B. Change in mean arterial blood pressure with increasing dose of mannitol is maintained within the range of normal mean arterial blood pressure.

TABLE 3 :

ARTERIAL BLOOD GAS ANALYSIS - PH :

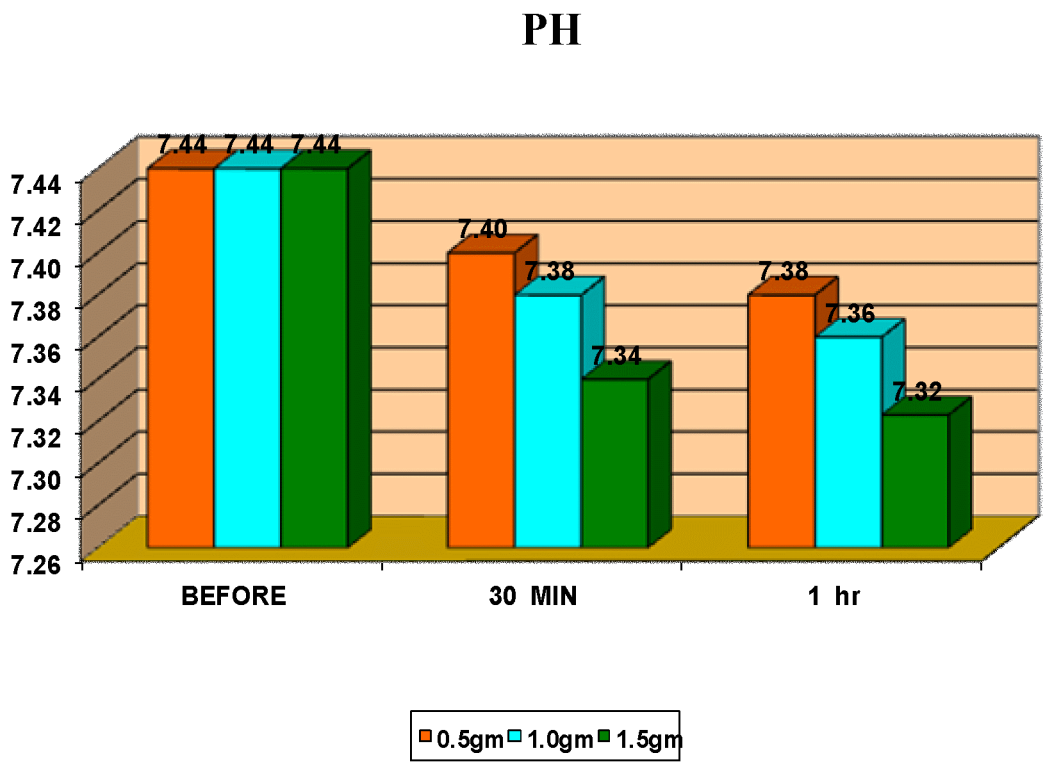
20% MANNITOL	BEFORE	30 MIN	1 HR
0.5GM	7.44	7.40	7.38
1.0GM	7.44	7.38	7.36
1.5GM	7.44	7.34	7.32
P' VALUE	1.00 NS	< 0.001 SIG	< 0.001 SIG

A. In this arterial blood gas analysis - PH, P value is less than 0.005

B. There is significant change in arterial blood gas analysis – PH value with increasing dose of mannitol .

CHART 3 :

ARTERIAL BLOOD GAS ANALYSIS - PH :



A. There is significant change in arterial blood gas analysis – PH value with increasing dose of mannitol .

B. Change in arterial blood gas analysis – PH value with increasing dose of mannitol is maintained within the acceptable range of arterial blood gas analysis – PH value .

TABLE 4 :

ARTERIAL BLOOD GAS ANALYSIS - SODIUM :

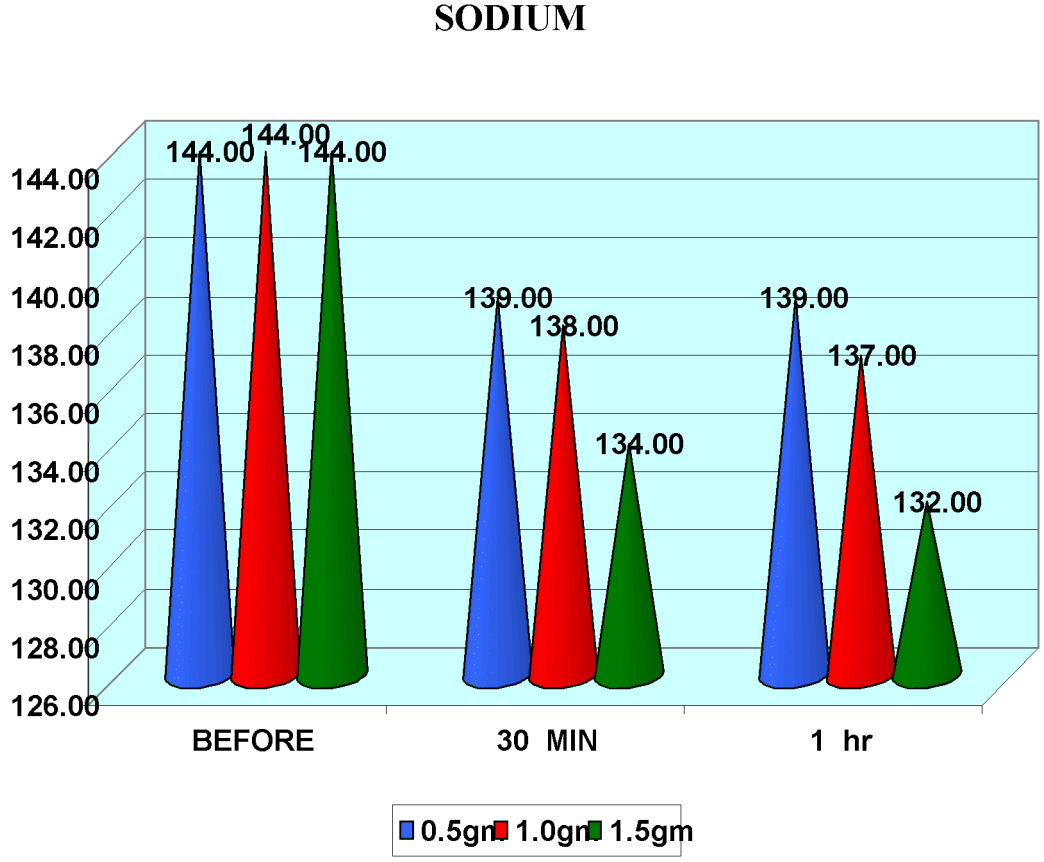
20% MANNITOL	BEFORE	30 MIN	1 HR
0.5gm	144.00	139.00	139.00
1.0gm	144.00	138.00	137.00
1.5gm	144.00	134.00	132.00
p' value	1.00 NS	< 0.001 Sig	< 0.001 Sig

A. In this arterial blood gas analysis - sodium , P value is less than 0.005

B. There is significant change in arterial blood gas analysis – sodium value with increasing dose of mannitol .

CHART 4 :

ARTERIAL BLOOD GAS ANALYSIS - SODIUM :



A. There is significant change in arterial blood gas analysis – sodium value with increasing dose of mannitol .

B. Change in arterial blood gas analysis – sodium value with increasing dose of mannitol is maintained within the acceptable range of arterial blood gas analysis – sodium value .

TABLE 5 :

ARTERIAL BLOOD GAS ANALYSIS – POTASSIUM:

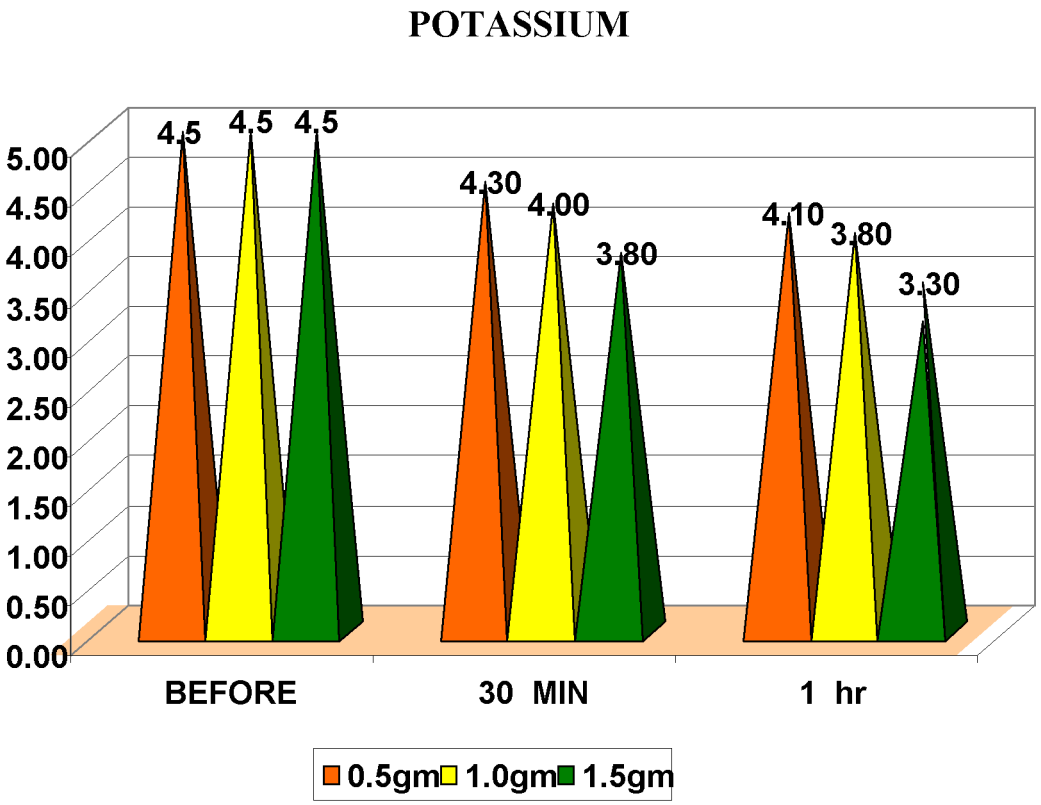
20% MANNITOL	BEFORE	30 MIN	1 HR
0.5GM	4.50	4.30	4.10
1.0GM	4.50	4.00	3.80
1.5GM	4.50	3.80	3.30
P' VALUE	1.00 NS	< 0.001 SIG	< 0.001 SIG

A. In this arterial blood gas analysis - potassium , P value is less than 0.005

B. There is significant change in arterial blood gas analysis – potassium value with increasing dose of mannitol .

CHART 5 :

ARTERIAL BLOOD GAS ANALYSIS POTASSIUM:



A. There is significant change in arterial blood gas analysis – potassium value with increasing dose of mannitol .

B. Change in arterial blood gas analysis – potassium value with increasing dose of mannitol is maintained within the acceptable range of arterial blood gas analysis – potassium value .

TABLE 6 :

ARTERIAL BLOOD GAS ANALYSIS – ANION GAP :

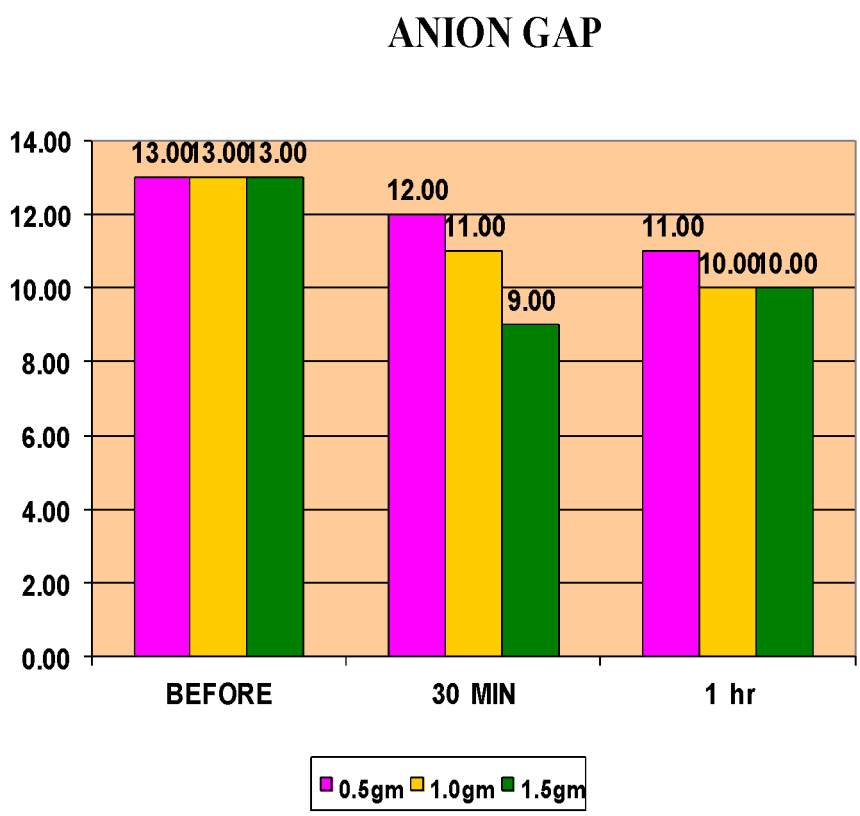
20% MANNITOL	BEFORE	30 MIN	1 HR
0.5GM	13.00	12.00	11.00
1.0GM	13.00	11.00	10.00
1.5GM	13.00	9.00	10.00
P' VALUE	1.00 NS	< 0.001 SIG	< 0.001 SIG

A. In this arterial blood gas analysis – Anion Gap, P value is less than 0.005

B. There is significant change in arterial blood gas analysis – Anion Gap value with increasing dose of mannitol .

CHART 6 :

ARTERIAL BLOOD GAS ANALYSIS – ANION GAP :



A. There is significant change in arterial blood gas analysis – Anion Gap value with increasing dose of mannitol .

B. Change in arterial blood gas analysis – Anion Gap value with increasing dose of mannitol is maintained within the acceptable range of arterial blood gas analysis – Anion Gap value .

TABLE 7 :

URINE OUTPUT :

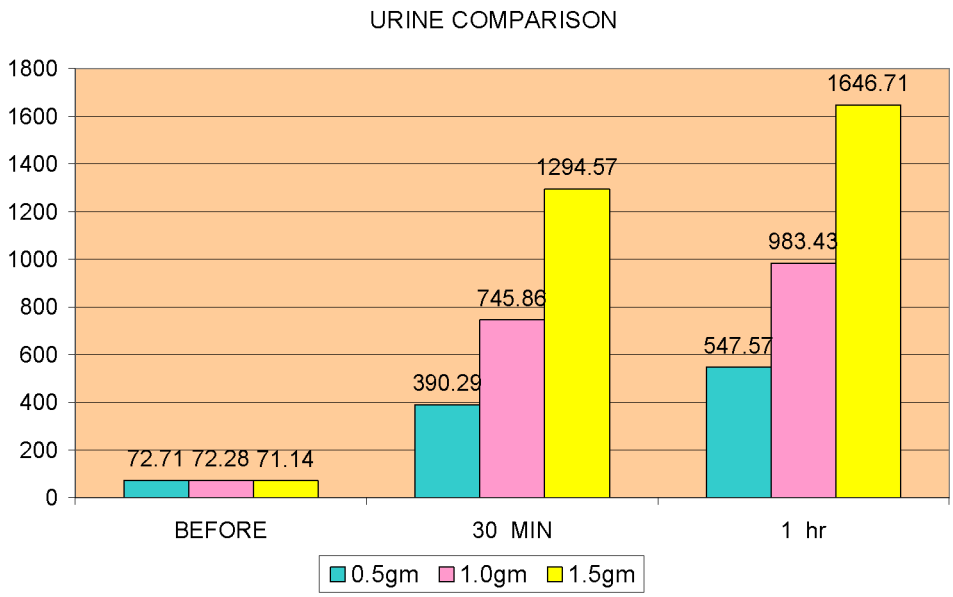
20% MANNITOL	BEFORE	30 MIN	1 HR	P' VALUE
0.5GM	72.71	390.29	547.57	< 0.001
1.0GM	72.28	745.86	983.43	< 0.001
1.5GM	71.14	1294.57	1646.71	< 0.001

A. In this urine output –, P value is less than 0.005

B. There is significant change in urine output value with increasing dose of mannitol .

CHART 7 :

URINE OUTPUT :



A. There is significant change in urine output value with increasing dose of mannitol .

B. Change in urine output value with increasing dose of mannitol is maintained within the acceptable range without disturbing serum electrolytes and haemodyanamic stability.

TABLE 8 :

TEMPERATURE :

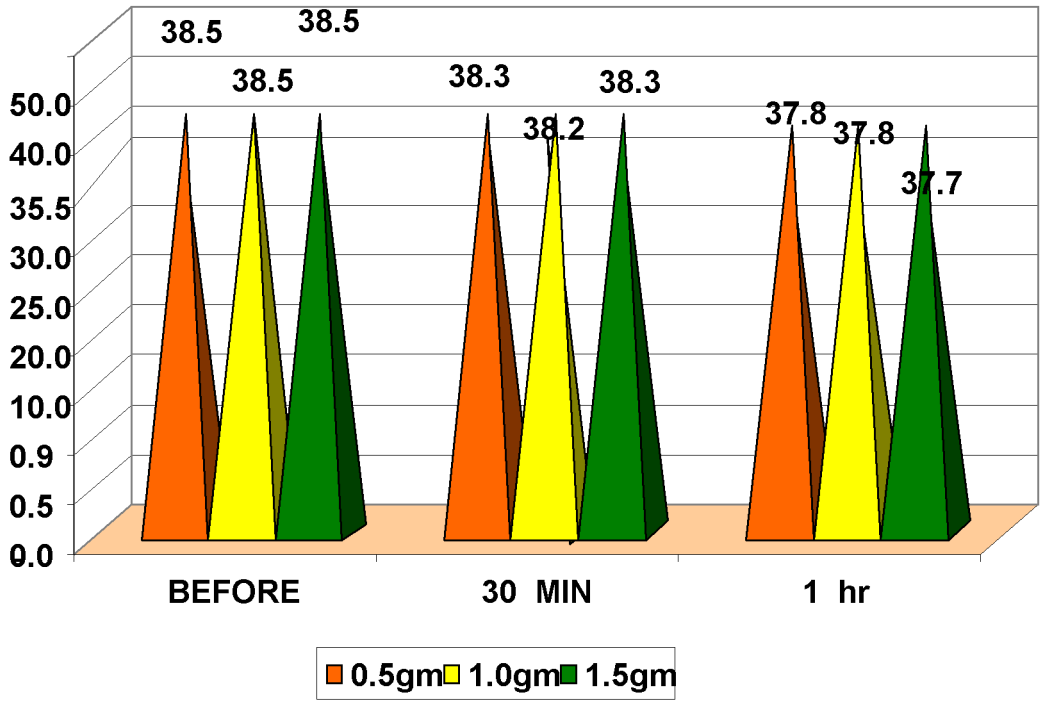
20% MANNITOL	BEFORE	30 MIN	1 HR
0.5GM	38.5	38.3	37.8
1.0GM	38.5	38.2	37.7
1.5GM	38.5	38.3	37.8
P' VALUE	1.00 NS	0.80 NS	0.90 NS

A. In this Temperature Measurement P value is more than 0.005

B. There is no significant in change in temperature.

Chart 8 :

TEMPERATURE :



A. There is no significant change in temperature with increasing dose of mannitol .

B. Change in temperature with increasing dose of mannitol is statistically not significant .

TABLE 9 :

AGE :

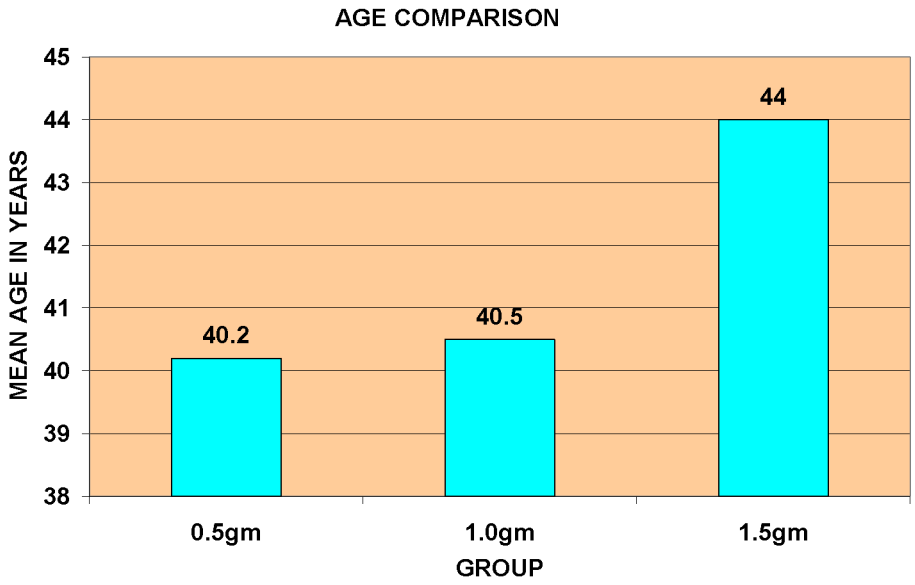
20% MANNITOL	BEFORE	30 MIN	1 HR	P' VALUE
0.5GM	40.2	40.2	40.2	1
1.0GM	40.5	40.5	40.5	1
1.5GM	44	44	44	1

A. In this age distribution, P value is 0.344 which is more than 0.005.

B. Age distribution shows statistically not significant difference.

CHART 9 :

AGE :



A. Age distribution shows statistically not significant difference.

TABLE 10 :

SEX :

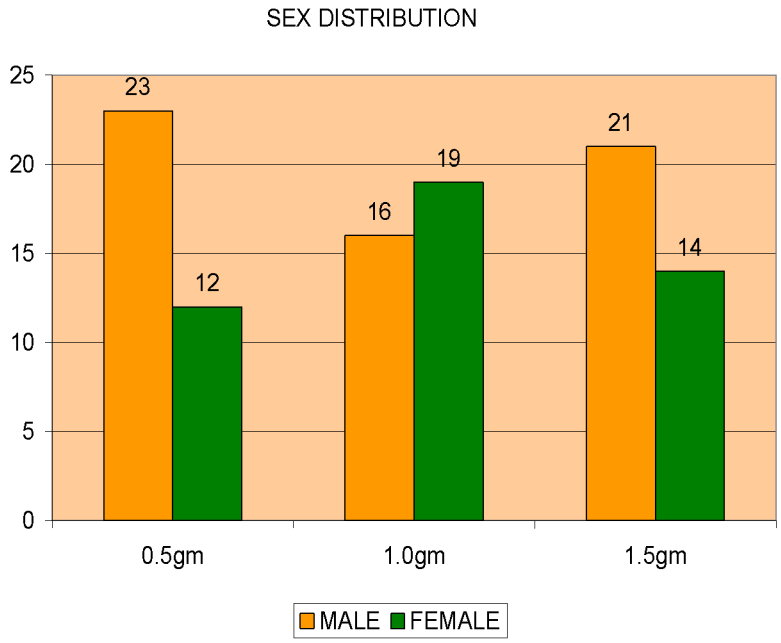
20% MANNITOL	**BEFORE**		**30 MIN**		**1 hr**	
SEX	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
0.5gm	23	12	23	12	23	12
1.0gm	16	19	16	19	16	19
1.5gm	21	14	21	14	21	14

A. In this sex distribution, P value is 0.653 which is more than 0.005.

B. Sex distribution shows statistically not significant difference.

CHART 10 :

SEX :



A. Sex distribution shows statistically not significant difference.

TABLE 11 :

BODY MASS INDEX MEASUREMENT:

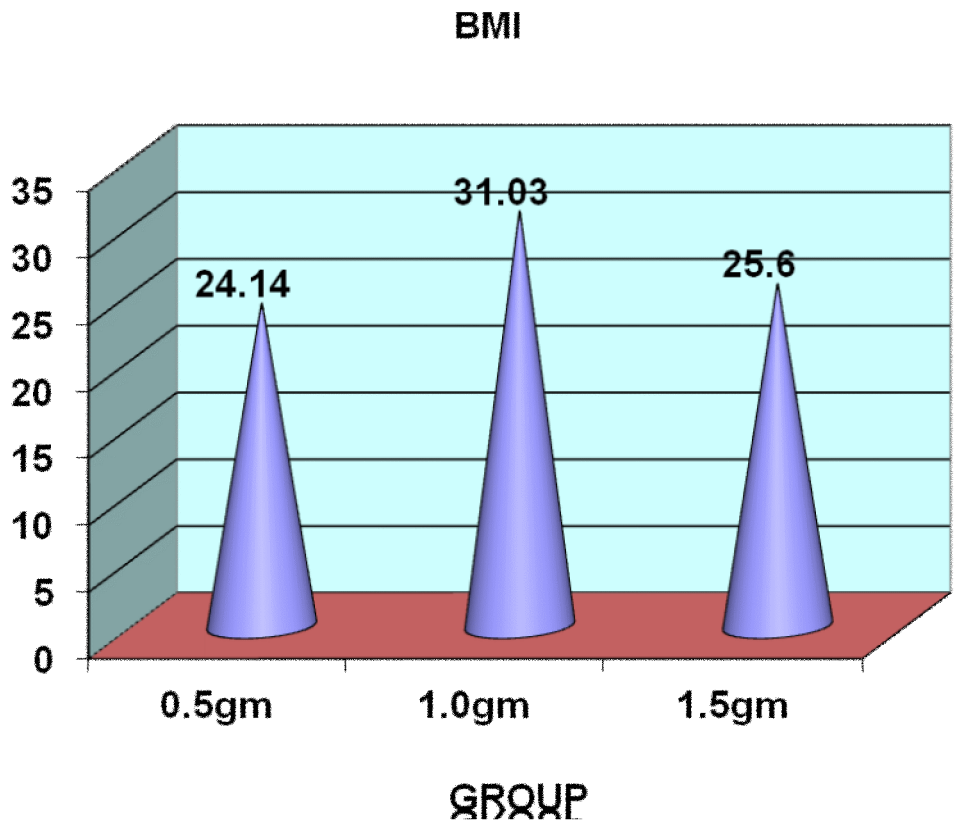
20% MANNITOL	BEFORE	30 MIN	1 hr	'p' value
0.5gm	24.14	24.14	24.14	1
1.0gm	31.03	31.03	31.03	1
1.5gm	25.6	25.6	25.6	1

A. In this Body mass index measurement , P value is 0.403 which is more than 0.005.

B. Body mass index measurement shows statistically not significant difference.

CHART 11 :

BODY MASS INDEX MEASUREMENT :



A. Body mass index measurement shows statistically not significant difference.

DISCUSSION

Mannitol is often recommended as the first-choice hyperosmotic drug to treat increased intracranial pressure (ICP) and alleviate brain bulk during intracranial surgery. However, the optimal administration and dosage of mannitol for brain relaxation remain controversial, especially in patients with preoperative increased ICP. A common routine dose is frequently chosen for a given surgical procedure regardless of the size of the lesion and the mass effect that results.

Previous prospective randomized trials have focused on the relationship between mannitol and intraoperative brain relaxation; however, none of these trials examined how different doses of mannitol influenced brain relaxation in patients with a preoperative brain midline shift.

The main side effects of mannitol include electrolyte abnormalities (for example, hypokalemia) and renal and cardiac dysfunction. Patients with heart failure, pulmonary edema, electrolyte imbalance, chronic hypertension, coronary heart disease, and diabetes often have renal dysfunction without clinical manifestations. Mannitol

can exacerbate this dysfunction and lead to kidney injury . Cardiac preload and central venous pressure increase 5 to 15 min after mannitol is administered. The diuretic effects of mannitol may cause water and electrolyte imbalances, hypotension, and decreased plasma concentrations of sodium, potassium, and chlorine. As shown in other studies, increased doses of mannitol resulted in an increase in osmolarity, a decrease in serum sodium concentration, and an increase in urine output.

The development of hyponatremia can be explained by the changes in osmolarity and the initial volume shift toward the intravascular compartment along the osmolar gradient and the resulting hemodilution. Higher doses of mannitol result in a dose-related increase in osmolarity, as well as a similar dose-related decrease in brain water content; this results in better relaxation scores in patients with traumatic brain injury.

Manninen et al described a significant increase in the serum potassium level, which reached a maximum mean increase of 1.5 mmol/L, after high-dose mannitol (1.5 g/kg) administration in seven patients undergoing cerebral aneurysm clipping. Therefore, patients

should be closely and carefully observed for side effects, especially patients who receive a large dose of mannitol and/or have preoperative increased intracranial pressure.

During the operation, the neurosurgeon will decide whether to initiate treatment for brain bulk via the assessment of intraoperative brain relaxation, which is not an objective sign, such as intracranial pressure. Treatments for improving brain relaxation include adjusting the ventilator to induce hyperventilation, expanding the surgical incision site, and infusing mannitol; these procedures contribute to tumor exposure and excision. Thus, the subjective assessment of the degree of brain relaxation can be used as a diagnostic criterion prior to treatment. Monitoring intracranial pressure or cerebral water content is not routine during brain tumor resection because the extra invasive monitoring of patients increases the risk of brain herniation.

Sorani et al. performed a retrospective study to characterize the dose–response relationship between mannitol and ICP in intensive care unit patients with traumatic brain injury and found that the degree and incidence of peritumoral edema greatly varied. Therefore, it is not appropriate to measure the effect of mannitol in patients with

supratentorial tumors, including gliomas and meningiomas, using brain water content.

In this prospective randomized trial, we will observe the effects of different doses of mannitol on patient outcomes three months postoperatively. Patients undergoing craniotomy commonly have complications that include postoperative cerebral edema, cerebral hemorrhage, recurrence, and even death, which are closely related to intraoperative tumor exposure, resection, and sufficient coagulation. The incidence of postoperative complications determines the length of intensive care unit and hospital stay, as well as patient outcome. Mannitol may help improve tumor exposure and resection. However, if the BBB is damaged, mannitol will be transferred from the ruptured or highly permeable blood vessels into brain tissue, which reverses the osmotic pressure difference and results in brain edema. Animal studies demonstrate that five repeated doses of mannitol lowered ICP and reduced cerebral edema; however, edema increased following greater exposure to mannitol.

Based on the current literature, we propose that different doses of mannitol will improve brain relaxation, as well as ease surgical exposure in a dose-dependent manner for patients with preoperative midline shift undergoing elective supratentorial brain tumor surgery.

The risk of brain swelling after dural opening is high in patients with midline shift undergoing supratentorial tumor surgery. Brain swelling may result in increased intracranial pressure, impeded tumor exposure, and adverse outcomes.

Mannitol is recommended as a first-line dehydration treatment to reduce brain edema and enable brain relaxation during neurosurgery. Research has indicated that mannitol enhanced brain relaxation in patients undergoing supratentorial tumor surgery; however, these results need further confirmation, and the optimal mannitol dose has not yet been established. We propose to examine whether different doses of 20% mannitol improve brain relaxation in a dose-dependent manner when administered at the time of incision.

Quentin et al examined the effects of two doses (0.5 and 1.5 g/kg) of mannitol on brain relaxation in tumor patients, neither of which was the routine clinical dose (1 g/kg); additionally, they did not

consider the effect of preoperative intracranial mass. However, these studies indicated that the effect of mannitol on brain relaxation was dose-dependent and higher doses 1.5gm/kg of body weight gives better brain relaxation than lower dose of 0.5gm / kg of body weight of 20% mannitol. The current proposal is a prospective randomized controlled study that aims to examine the effects of three doses of mannitol on brain relaxation in patients with preoperative midline shift.

Dose–response relationship of mannitol and intracranial Pressure:

After decades of work, it is surprising that a dose–response curve for mannitol has not been determined, particularly given that it is one of the few agents used to treat elevated ICP. Although many individual studies have shown that mannitol decreases ICP, taken together, the data from our nonparametric analysis of the literature and the wide 95% confidence interval in the dose–response meta-regression suggest that varying dosage has an undefined effect on decrease in ICP. In fact, the literature suggests that icp Decrease depends more strongly on mannitol's administration Protocol—specifically the ICP level at the time the dose is given—than on dose.

Although contemporary studies may demonstrate a more complete understanding of Physiology and molecular biology, they sometimes lack the large patient sample sizes and quantitative models of earlier Studies. Moreover, recent studies in which the authors have compared the effects of other ICP treatments with mannitol are doing so without complete knowledge of mannitol's dose and time-dependent effects. More comprehensive Studies are needed to definitively address the question of mannitol dose response. These studies could further

elucidate. The relationships among parameters related to ICP management, enable more precise use of mannitol, and improve patient outcomes.

A CHRONOLOGICAL REVIEW :

Mannitol dose–response studies in the 1970s and 1980swere often large and followed mannitol administration protocols requiring ICP of 25 mmhg. These included 2 Studies each by James and colleagues and Mcgraw and colleagues containing 48, 60, 150, and 61 patients. James measured a peak ICP reduction at 44 minutes but saw no relationship between dose and rapidity of peak response. This author also reported that return to baseline ICP was unpredictable but related to the initial ICP and that doses, 1 g/kg did not always reduce ICP. Mcgraw and Colleagues found that the level of ICP and the cumulative amount of preceding doses of mannitol influenced the response of ICP more than the dose of mannitol. They concluded that unnecessarily large doses or prophylactic doses could lead to more mannitol being required later. Marshall Et al. found that "smaller doses than those previously recommended were effective in reducing the ICP acutely."

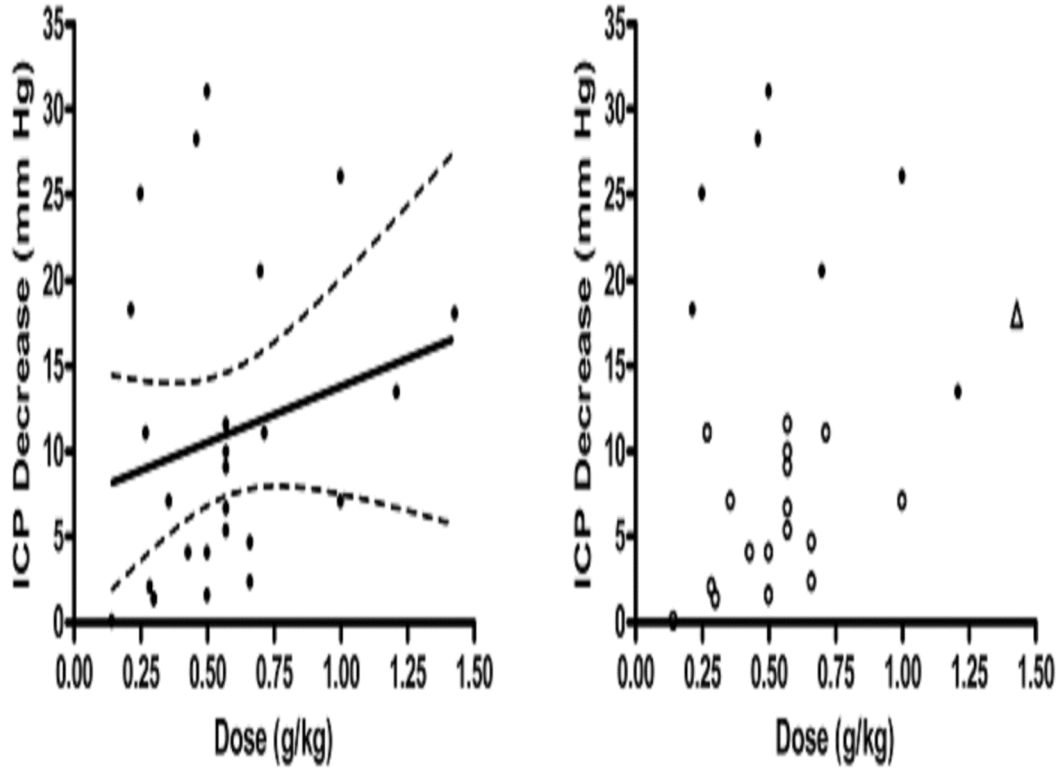
Several studies have been conducted since 1990. Authors Of these studies have lowered the minimum ICP threshold for mannitol administration, perhaps reflecting studies Showing that even ICP 15 mm hg can result in herniation. Overall, reporting of relevant dose response parameters has been more complete, with the exception of time to achieve minimum ICP. Clearly, the duration of the mannitol effect is critical when comparing doses or other ICP Treatments. Furthermore, these studies have typically included fewer patients, with the exception of Cruz et al. who studied preoperative high-dose mannitol but only reported daily average values, and Rosner et al who focused primarily on CPP management. of note, Hartl et al.11 Found that when initial ICP was 20 mm Hg, ICP did not change significantly during or after mannitol infusion, but with a preinfusion ICP 20 mm Hg, a decrease was seen.

CHALLENGES AND NEXT STEPS :

There are several challenges to constructing an ideal dose–response curve, as is commonly done in pharmacodynamic studies, based on retrospective clinical data. For example, mannitol doses are administered according to patient need, often as gross rather than weight-adjusted amounts, and doses at the low and high ends of the

range may not be administered because they are either not efficacious or may have adverse effects. High doses of mannitol Increase serum osmolality and have been associated with risk of renal failure. Also, height measurements needed to calculate ideal body weight are never reported. It is possible that some ICP readings captured particularly volatile periods or were incorrectly recorded given the low-resolution data collection tools that exist even today. Finally, it is clear that treatment protocols varied significantly among centers and over time, particularly given that this metaanalysis includes stroke and tumor patients as well as heterogeneous samples of patients with traumatic brain injury.

MANNITOL DOSE-ICP PRESSURE RESPONSE CURVE

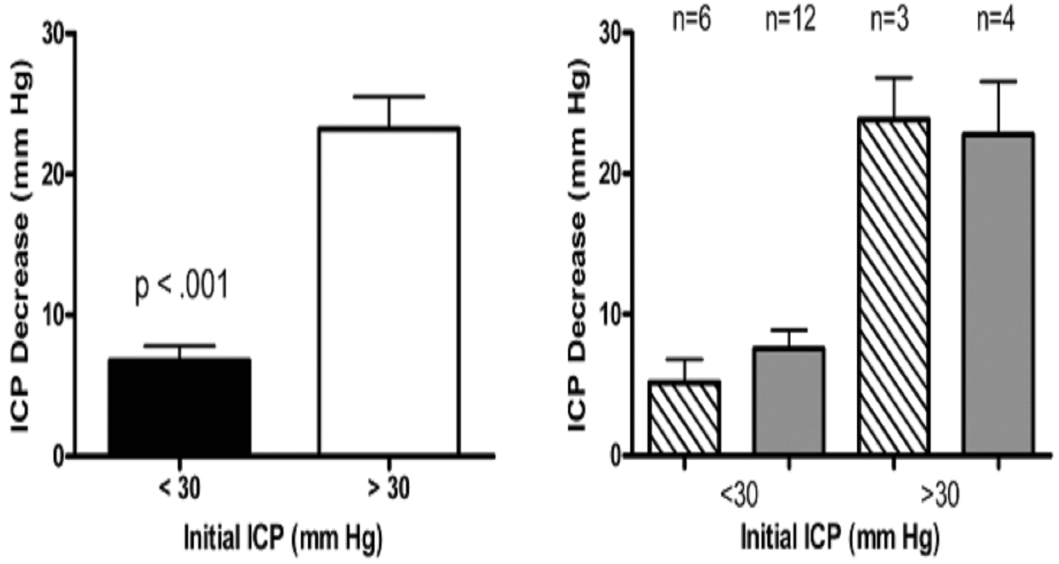


However, the impacts of these differences on the effects of mannitol cannot be determined. Well-designed, adequately-funded studies in which the authors record and report a broad set of data (gross dose amounts; time, sequence, duration, and interval of dose administration; physiological parameters such as ICP and CPP; metabolic markers such as osmolality and creatinine; and detailed patient characteristics

such as age, race, sex, weight, Glasgow coma scale score, and so on) will be crucial in defining the mannitol–ICP dose–response relationship and could also enable better future metaanalysis.

Comprehensive mathematical models based on continuously monitored physiological parameters are needed to elucidate the relationships between the treatments, vital signs, and outcomes in clinical care.

SIGNIFICANT DECREASE IN ICP WITH INCREASE IN MANNITOL DOSE



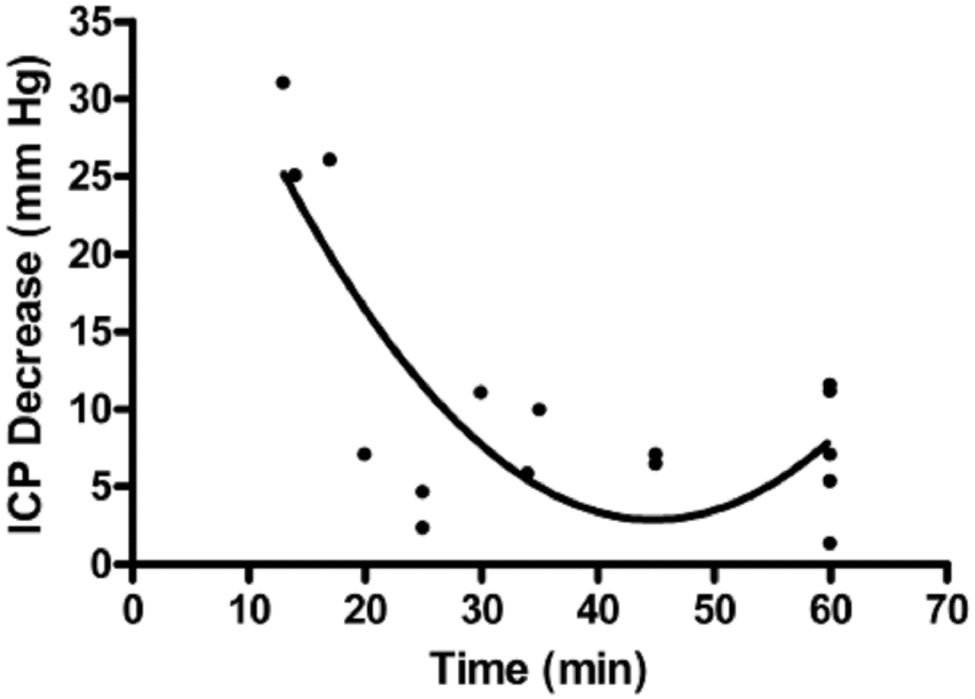
1. Increasing dose of mannitol gives decrease in icp in quick interval of time.
2. 20% Mannitol of 1.5gm / kg decreases icp in quick interval of time without affecting normal physiology and anatomy of brain.

Mannitol is the osmotic agent most commonly used to reduce brain mass after brain injury and stroke, yet its pharmacodynamics are still not understood. In fact, in sharp contrast with most other drugs used to treat common diseases (hypertension, diabetes, and so on), protocols such as dosage regimens and thresholds for treatment still vary widely. This metaanalysis aggregated data from studies that have

quantitatively characterized the dose–response relationship for mannitol and ICP. Our nonparametric analysis revealed that, although mannitol is always shown to reduce ICP, the quantitative relationship between dose and response is inconsistent. We found a weak linear relationship between change in ICP and mannitol dose. The lack of statistical significance and low R-square value could reflect the variation in protocols among studies or the variation in patients both within and among studies. However, we saw a strong relationship between ICP decrease and ICP levels at the time mannitol was given. Furthermore, ICP decreases were greatest shortly after doses were given, but there are limited data to support this conclusion. We also found that recent studies tend to enroll fewer patients and set a lower ICP threshold for mannitol administration but are more complete in their reporting of parameters of interest.

MANNITOL DOSE – TIME – ICP PRESSURE

RESPONSE CURVE



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Significant decrease in ICP with infusion of mannitol in high dosage with appropriate time. Mannitol infusion in quick interval gives significant fall in ICP than regular interval.

Surprisingly, after years of use, the nature of the mannitol Dose–response curve is still under debate. Moreover, Studies in which authors compare the effects of new ICP treatments with mannitol are undertaken with incomplete knowledge of mannitol's effects and

therefore risk drawing misleading conclusions. It is difficult to imagine reducing the variability in the clinical management of elevated ICP without fully understanding these fundamental pharmacodynamic Relationships. The metaanalysis presented here highlights the need for a consensus of methods and results required to determine this relationship.

SUMMARY OF THIS STUDY

This study was carried out at Government Rajaji Hospital, Madurai. After getting ethical committee approval and informed consent 48 patients of both sexes (male and female) who underwent elective craniotomy for supratentorial tumour surgeries under general anaesthesia divided into three groups as group-A group-B and group-C with 16 in each group.

ARMS	ASSIGNED INTERVENTIONS
GROUP A: III. 20% mannitol 0.5gm/kg IV. Study subjects will be randomized to receive an infusion of 20% mannitol 0.5gm/kg over 3o minutes after induction.	III. Drug: mannitol IV. Variation of mannitol dose.
GROUP B: III. 20% mannitol 1.0gm/kg IV. Study subjects will be randomized to receive an infusion of 20% mannitol 1.0gm/kg over 3o minutes after induction.	III. Drug: mannitol IV. Variation of mannitol dose.
GROUP C: III. 20% mannitol 1.5gm/kg IV. Study subjects will be randomized to receive an infusion of 20% mannitol 1.5gm/kg over 3o minutes after induction.	III. Drug: mannitol IV. Variation of mannitol dose.

In the preoperative waiting room detailed history and physical examination was done. Basic investigations were collected. Baseline data like pulse rate, blood pressure, mean arterial pressure, spo2, temperature, preoperative arterial blood gas were recorded. Group A, Group B and Group C were explained about the procedures and follow up pattern. A standardized anaesthetic technique was used.

All patients were premedicated with inj.glycopyrolate 0.2mg intramuscularly 45 minutes before surgery. Monitors were connected. Intravenous canula secured and connected to i.v. fluids. Another Intravenous canula secured for infusion of mannitol. Patients were preoxygenated with 100% O2 for 3 minutes. Patients were induced with injection fentanyl 2 micrograms per kilogram of body weight, injection thiopentone 5 milligram per kilogram of body weight, injection succinyl choline was avoided in my study, because to avoid rise in intracranial pressure. For that injection vecronium of 0.08 miligram per kilogram of body weight was used. To blunt the intubation response injection 2% lignocaine of 1.5mg/kilogram was given. Patients were intubated with 7/7.5 size endotracheal tube for female and 8/8.5 size endotracheal tube for male was used. Bilateral air entry checked and connected to closed circuit. Patient is maintained with N20:O2 in 2:2 with injection fentanyl 1 micrograms per kilogram

of body weight every 45 minutes and injection vecronium in titrated doses. ETCO2 was maintained in 25-30 mmHg range throughtout the procedure. Haemodyanamic variables like blood pressure, mean arterial pressure, pulse rate and spo2 were measured immediately prior to the infusion of mannitol, at 30 and 60minutes after the administration of mannitol. Similarly urine out put, perioperative fluid balance, blood loss and laboratory data like arterial blood PH, electrolytes were measured immediately prior to the infusion of mannitol, at 30 and 60 minutes after the administration of mannitol. Data were recorded according to the time frame. At the time opening duramater, Brain relaxation was assessed by a neuro surgeon on scale from 1 to 4 which was given as follows.

At the end of surgery, after adequate attempts of respiration patients were reversed with injection glycopyrolate of 10 micrograms per kilogram of body weight and injection neostigmine of 40 micrograms per kilogram of body weight. Adequate suctioning done. To blunt the extubation response injection 2% lignocaine of 1.5mg/kilogram was given Patients were then extubated after gaining adequate muscle power.

PARAMETERS MONITORED INTRAOPERATIVELY

PRIMARY OUTCOME MEASURES :

- Brain relaxation at the opening of the duramater assessed by a neuro surgeon on scale (ROZET QUENTIN scale) from 1 to 4.
- Scale 1: perfectly relaxed (shrunken dura with prominent veins)
- Scale 2: satisfactorily relaxed (only prominent veins)
- Scale 3: firm brain
- Scale 4: bulging brain
- Time frame : at the opening of the dura mater.

SECONDARY OUTCOME MEASURES :

- **Haemodynamic variables: -**

  Mean arterial pressure, Heart rate, Blood pressure, SPO2.

  Time frame - immediately prior to the infusion of mannitol, at 30 and 60minutes after the administration of mannitol.

- **Urine output :**

  Time frame - immediately prior to the infusion of mannitol,

  at 30 and 60 minutes after the administration of

  mannitol

- **Perioperative fluid balance and blood loss :**

  Time frame - immediately prior to the infusion of mannitol

  at 30 and 60 minutes after the administration of

  mannitol.

- **Laboratory data:**

  Blood PH, electrolytes.

  Time frame - immediately prior to the infusion of mannitol,

  at 30 and 60minutes after the administration of

  mannitol.

CONCLUSION

A. In this study, from the data and statistical analysis, it is concluded that 1.5mg/kg of 20% mannitol gives better brain relaxation scores than 0.5mg/kg of 20% mannitol and 1.0mg/kg of 20% mannitol.

B. Hemodynamic stability, blood electrolytes, PH, urine output are better maintained without gross impairment in 1.5mg/kg of 20% mannitol.

C. Age, Sex, Body mass index did not influence the study results.

BIBLIOGRAPHY

1. Bedford rf, morris l, jane ja: intracranial hypertension during surgery for supratentorial tumor: correlation with preoperative computed tomography scans.j.anesthanalg 1982, 61:430433.
2. Rasmussen m, bundgaard h, cold ge: craniotomy for supratentorial brain tumors: risk factors for brain swelling after opening the dura mater. J.neurosurg 2004, 101:621626
3. Berger s, schürer l, härtl r, messmer k, baethmann a: reduction of post-traumatic intracranial hypertension by hypertonic/hyperoncotic saline/dextran and hypertonic mannitol.j.neurosurgery 1995, 37:98-108.
4. Kaufmann am, cardoso er: aggravation of vasogenic cerebral edema by multiple-dose mannitol.j.neurosurg 1992, 77:584-589.
5. Wise bl: high-dose mannitol. J neurosurg 2004, 101:566-567.
6. Cruz j, minoja g, okuchi k, facco e: successful use of the new high-dose mannitol treatment in patients with glasgow coma scale scores of 3 and bilateral abnormal pupillary widening: a randomizedtrial.j.neurosurg 2004, 100:376-383.

7. Myburgh ja, lewis sb: mannitol for resuscitation in acute head injury: effects on cerebral perfusion and osmolality. Critical care resusc 2000, 2:14-18.

8. Sorani md, morabito d, rosenthal g, giacomini km, manley gt: characterizing the dose–response relationship between mannitol and intracranial pressure in traumatic brain injury patients using a high-frequency physiological data collection system.j.neurotrauma 2008, 25:291-298.

9. Rozet i, tontisirin n, muangman s, vavilala ms, souter mj, lee la, kincaid ms, britz gw, lam am: effect of equiosmolar solutions of mannitol versus hypertonic saline on intraoperative brain relaxation and electrolyte balance. Anesthesiology 2007, 107:697-704.

10. Wu ct, chen lc, kuo cp, ju dt, borel co, cherng ch, wong cs: a comparison for 3% hypertonic saline and mannitol for brain relaxation during elective supratentorial brain tumor surgery.anesthanalg 2010, 110:903-907.

11. Quentin c, charbonneau s, moumdjian r, lallo a, bouthilier a, fournier-gosselin mp, bojanowski m, ruel m, sylvestre mp, girard f: a comparison of two doses of mannitol on brain

relaxation during supratentorial brain tumor craniotomy: a randomizedtrial.anesthanalg 2013, 116:862-868.

12. Starke rm, dumont as: the role of hypertonic saline in neurosurgery.world neurosurg 2013.

13. Todd mm, warner ds, sokoll md, maktabi ma, hindman bj, scamman fl, kirschner j: a prospective, comparative trial of three anesthetics for elective supratentorial craniotomy: propofol/fentanyl, isoflurane/nitrous oxide, and fentanyl/nitrous oxide.anesthesiology 1993, 78:1005-1020.

14. wma declaration of helsinki - ethical principles for medical research involving human .

15. Ministry of health, the people's republic of china: ethics review for biomedical research involving humans (trial). Bull repub chin minist health 2007.

16. Council for international organizations of medical sciences: international ethical guidelines for biomedical research involving human subjects.bull med ethics 2002, 182:17-23

17. Kazner e, lanksch w, steinhoff h, wilske j: computerized axial tomography of the skull - diagnostic possibilities and clinical results.

18. Fortschr neurol psychiatr grenzgeb 1975, 43:487-574.
19. Cohen j: statistical power analysis for the behavioral sciences. Hillsdale: lawrence erlbaum associates; 1988.
20. Brain trauma foundation, american association of neurological surgeons, congress of neurological surgeons: guidelines for the management of severe traumatic brain injuryj neurotrauma 2007, 24(suppl 1):s1-s106.
21. Du zq, wang hy: application of mannitol in patients with cerebrovascular diseases. Chin j cerebrovasc dis 2008, 2:349-350.
22. Shen y: prevention and treatment of mannitol-induced acute renal injury. J appl clin pediatr 2010, 25:309-311.
23. Chatterjee n, koshy t, misra s, suparna b: changes in left ventricular preload, afterload, and cardiac output in response to a single dose of mannitol in neurosurgical patients undergoing craniotomy: a transesophageal echocardiographic study.j.neurosurganesthesiol 2012, 24:25-29
24. Manninen ph, lam am, gelb aw, brown sc: the effect of high dose mannitol on serum and urine electrolytes and osmolality in neurosurgical patients.j anaesth 1987, 34:442-446.

25. Hirota k, hara t, hosoi s, sasaki y, hara y, adachi t: two cases of hyperkalemia after administration of hypertonic mannitol during craniotomy.j anesth 2005, 19:75-77.

26. Todd mm, cutkomp j, brian je: influence of mannitol and furosemide, alone and in combination, on brain water content after fluid percussion injury.anesthesiology 2006, 105:1176-1181.

27. Olsen ts, langhorne p, diener hc, hennerici m, ferro j, sivenius j, wahlgren ng, bath p, european stroke initiative executive committee: european stroke initiative recommendation for stroke management-update 2003.cerebrovasc dis 2003, 16:311-337.

PROFORMA

Name :

I.P.No :

Age & Sex :

Weight:

Date of Admission : Date of Discharge :

Diagnosis :

Procedure :

Professor : Asst.Prof :

Neuro Surgeon Dr : Neuro Surgeon Dr :

History of Present Illness :

History of Past Illness:

Drug History : Hypertension / Diabetes / Asthmatic / Seizure Disorder / Head Injury / ENT Bleed / Bleeding Disorders

General Examination :

Body Built And Nutritional Status :

Examination :

Temperature : Hydration : Mouth :

Pulse : / Min Icterus : Yes / No Dental :

Bp : Mmhg Anaemia : Yes / No

Respiration : / Min Cyanosis : Yes / No Spine :

Spo2 : % Clubbing : Yes / No Mpg : 1 / 2 / 3 / 4

Urineoutput : ml Edema : L / G : Yes / No

Venous Access Site : Jvp : Normal/Abnormal

System Examination :

CVS : RS : ABD : CNS :

Gcs – E / V / M Pupils: Rt /Lt /Srl /Brl /Abnormal

Neurological Deficit IfAny: Others :

Basic Investigations :

Hb : Gm% Electrolytes – Na / K / Cl / Urea : gm

Creatinine : Mg

ABG : Ph- / / Hco3- / Be- / Anion Gap-

Blood Sugar- R / F / Pp : mg % Bl.Grp : Bt : Ct :

Urine –R:

Special Investigations:

ECG : Echo : X-ray Chest :

Ct Brain P/C: MRI P / C :

Asa Grade : 1 / 2 / 3 / 4

Anaesthesia Procedure :

Premedication : Induction Agents :

Maintenance : Reversal

Agents:

Elective Ventilation:

PRIMARY OUTCOME MEASURES :

Brain relaxation at the opening of the dura mater assessed by a senior neurosurgeon on a scale (ROZET QUENTIN scale) from 1 to 4.

Time frame : At the opening of the dura mater.

SCALES	perfectly relaxed (shrunken dura with prominent veins)	satisfactorily relaxed (only prominent veins)	firm brain	bulging brain
SCORES	1	2	3	4

SECONDARY OUTCOME MEASURES :

TIME	PH	NA	K	A.G	URINE OUTPUT
30 min BEFORE MANNITOL ADMINISTRATION					
AFTER MANNITOL ADMINISTRATION					
30 MIN					
60 MIN					

BEFORE MANITOL ADMINISTRATION

	name	IP No.	age	sex	bmi	Urine(ml)	relaxation score	HR	SYST BP	DIAST BP	MAP	PH	PO2	PCO2	sodium	potassium	anion gap
	Group A																
1	Mariappan	11258	22	m	23	60	4	63	156	106	122.7	7.44	145	31	145	3.5	13
2	Selva raj	11320	32	m	24	75	4	56	142	110	120.7	7.43	152	30	135	3.5	15
3	Ilayaraja	11345	35	m	22	55	4	69	132	90	104.0	7.45	140	30	136	3.6	14
4	Prakash	11360	38	m	28	60	3	63	142	103	116.0	7.42	152	28	138	3.4	16
5	Fatima	11378	45	f	26	70	3	65	142	100	114.0	7.35	152	26	145	3.5	11
6	Pandeeswari	11425	49	f	20	95	3	69	145	105	118.3	7.38	162	25	145	3.6	10
7	Kalaiselvan	11446	52	m	34	80	3	62	145	98	113.7	7.34	150	26	144	3.5	12
8	Kumaran	11449	53	m	25	75	4	65	125	103	110.3	7.42	125	24	132	3.9	11
9	Raja	11528	55	m	26	65	4	65	180	110	133.3	7.46	142	23	135	3.8	9
10	Dhanalakshmi	11569	34	f	21	90	4	75	145	108	120.3	7.33	142	29	136	3.7	11
11	amutha	11635	44	f	22	85	3	85	162	106	124.7	7.36	152	32	135	3.5	13
12	Sukumar	11639	34	m	28	55	3	95	142	110	120.7	7.45	142	31	145	3.4	13
13	Rajan	11700	23	m	29	60	4	65	154	98	116.7	7.44	142	28	144	3.6	14
14	Brindha	11712	34	f	25	80	4	72	142	96	111.3	7.35	152	29	132	3.2	15
15	Mandaiyan	11715	45	m	27	95	4	71	155	96	115.7	7.36	142	28	133	3.6	12
16	Kaliappan	11768	56	m	26	100	4	70	125	105	111.7	7.42	152	28	139	3.9	13
	Group b																
1	gurunathan	11789	23	m	23	55	3	68	135	100	111.7	7.36	142	30	134	4.5	12
2	Selvan	11800	34	m	24	75	3	69	135	98	110.3	7.35	142	30	124	3.5	13
3	Ganapathy	11804	35	m	25	70	2	63	138	98	111.3	7.35	152	30	145	3.8	16
4	Guruvan	11836	45	m	26	85	3	78	139	95	109.7	7.36	154	30	142	3.9	15
5	alagarsamy	11842	46	m	23	80	3	85	134	97	109.3	7.35	154	32	14	3.7	14
6	Sindhu	11856	56	f	21	85	3	95	146	102	116.7	7.34	154	31	142	3.6	12
7	Ilakkiya	11860	57	f	22	80	3	85	143	91	108.3	7.35	124	30	135	3.8	13
8	Muthulakshmi	11869	60	f	25	55	3	84	150	101	117.3	7.36	154	29	134	3.4	15
9	Chinathai	11921	26	f	26	60	3	75	135	110	118.3	7.44	135	28	136	3.9	14
10	Phelix rani	11935	27	f	24	80	3	85	153	95	114.3	7.42	165	27	139	4.5	12
11	Sharmila Devi	11944	28	f	23	85	3	84	184	120	141.3	7.32	142	29	135	4.6	15
12	Parvathi	11956	29	f	21	65	3	96	145	100	115.0	7.44	154	29	138	4.5	12
13	Sudalai	11978	30	m	22	90	2	84	135	94	107.7	7.45	154	28	137	4.3	13
14	Shanthi	11990	35	f	21	85	3	75	135	90	105.0	7.45	154	27	135	4.1	16
15	alagar	11994	36	m	20	60	3	85	136	98	110.7	7.42	154	23	134	4.2	15
16	Baskaran	12003	37	m	22	75	3	59	130	95	106.7	7.41	124	29	132	4.1	14
	Group c																
1	Karuppu	12009	32	m	25	65	1	69	96	60	72.0	7.45	145	27	132	3.1	10
2	Kumar	12056	43	m	26	55	1	82	88	56	66.7	7.36	145	27	138	3.3	13
3	Velan	12152	54	m	28	75	1	71	92	48	62.7	7.37	145	28	137	3.5	10
4	Thamaraiselvan	12168	56	m	24	50	1	72	96	72	80.0	7.34	185	29	131	3.4	12
5	Kalian	12180	57	m	23	60	1	62	90	62	71.3	7.38	195	29	134	3.3	11
6	Senkathir	12196	59	m	26	75	1	68	95	54	67.7	7.37	124	29	135	3.5	12
7	Venkatesh	12199	23	m	25	55	1	63	96	62	73.3	7.36	154	28	136	3.6	10
8	Muthulakshmi	12201	35	f	21	85	1	62	95	61	72.3	7.35	154	26	135	3.5	9
9	Dhanalakshmi	12209	46	f	23	75	1	62	94	68	76.7	7.39	154	29	136	3.6	10
10	amutha	12220	56	f	25	95	1	68	90	62	71.3	7.35	145	31	134	3.2	10
11	Mukesh	12234	57	m	29	60	1	65	86	65	72.0	7.32	145	30	132	3.3	12

12	Amaravathy	12248	52	f	28	70	2	62	92	56	68.0	7.5	145	30	136	3.1	12
13	Kathiravan	12260	54	m	26	55	1	61	91	54	66.3	7.36	147	29	136	3.2	13
14	Kavitha	12289	34	f	22	95	1	63	95	60	71.7	7.33	147	28	135	3.5	10
15	Anand	12421	32	m	21	75	1	62	90	62	71.3	7.34	145	28	135	3.6	10
16	Pandeeswari	12560	43	f	19	60	1	61	92	58	69.3	7.36	168	29	134	3.5	9

30 MINUTES AFTER MANNITOL ADMINISTRAION

	name	IP No.	age	sex	bmi	Urine (ml)	*relaxation score*	*HR*	*SYST BP*	*DIAST BP*	*MAP*	*PH*	PO2	PCO2	*sodium*	*potassium*	*anion gap*
group a																	
1	Mariappan	11258	22	m	23	350	4	74	145	110	121.7	7.44	145	31	145	3.5	13
2	Selva raj	11320	32	m	24	415	4	84	142	101	114.7	7.43	152	30	135	3.5	15
3	Ilayaraja	11345	35	m	22	400	4	75	132	96	108.0	7.45	140	30	136	3.6	14
4	Prakash	11360	38	m	28	320	3	85	142	90	107.3	7.42	152	28	138	3.4	16
5	Fatima	11378	45	f	26	440	3	74	142	100	114.0	7.35	152	26	145	3.5	11
6	Pandeeswari	11425	49	f	20	355	3	84	134	110	118.0	7.38	162	25	145	3.6	10
7	Kalaiselvan	11446	52	m	34	315	3	92	145	98	113.7	7.34	150	26	144	3.5	12
8	Kumaran	11449	53	m	25	360	4	92	125	103	110.3	7.42	125	24	132	3.9	11
9	Raja	11528	55	m	26	410	4	70	180	105	130.0	7.46	142	23	135	3.8	9
10	Dhanalakshmi	11569	34	f	21	370	4	68	145	108	120.3	7.33	142	29	136	3.7	11
11	amutha	11635	44	f	22	415	3	65	162	110	127.3	7.36	152	32	135	3.5	13
12	Sukumar	11639	34	m	28	385	3	75	142	110	120.7	7.45	142	31	145	3.4	13
13	Rajan	11700	23	m	29	390	4	84	154	102	119.3	7.44	142	28	144	3.6	14
14	Brindha	11712	34	f	25	400	4	72	142	100	114.0	7.35	152	29	132	3.2	15
15	Mandaiyan	11715	45	m	27	410	4	71	130	96	107.3	7.36	142	28	133	3.6	12
16	Kaliappan	11768	56	m	26	380	4	70	125	105	111.7	7.42	152	28	139	3.9	13
group b																	
1	gurunathan	11789	23	m	23	675	3	56	136	96	109.3	7.36	142	30	134	4.5	12
2	Selvan	11800	34	m	24	840	3	58	135	94	107.7	7.35	142	30	124	3.5	13
3	Ganapathy	11804	35	m	25	825	2	92	136	98	110.7	7.35	152	30	145	3.8	16
4	Guruvan	11836	45	m	26	710	3	78	139	92	107.7	7.36	154	30	142	3.9	15
5	alagarsamy	11842	46	m	23	690	3	84	134	97	109.3	7.35	154	32	14	3.7	14
6	Sindhu	11856	56	f	21	725	3	82	143	96	111.7	7.34	154	31	142	3.6	12
7	Ilakkiya	11860	57	f	22	825	3	84	143	91	108.3	7.35	124	30	135	3.8	13
8	Muthulakshmi	11869	60	f	25	755	3	81	135	101	112.3	7.36	154	29	134	3.4	15
9	Chinathai	11921	26	f	26	670	3	76	135	98	110.3	7.44	135	28	136	3.9	14
10	Phelix rani	11935	27	f	24	780	3	75	153	95	114.3	7.42	165	27	139	4.5	12
11	Sharmila Devi	11944	28	f	23	830	3	78	184	96	125.3	7.32	142	29	135	4.6	15
12	Parvathi	11956	29	f	21	760	3	82	145	92	109.7	7.44	154	29	138	4.5	12
13	Sudalai	11978	30	m	22	695	2	78	135	94	107.7	7.45	154	28	137	4.3	13
14	Shanthi	11990	35	f	21	785	3	81	135	105	115.0	7.45	154	27	135	4.1	16
15	alagar	11994	36	m	20	815	3	76	132	98	109.3	7.42	154	23	134	4.2	15
16	Baskaran	12003	37	m	22	835	3	82	130	95	106.7	7.41	124	29	132	4.1	14

group c																	
1	Karuppu	12009	32	m	25	1160	1	82	92	65	74.0	7.45	145	27	132	3.1	10
2	Kumar	12056	43	m	26	1310	1	74	90	63	72.0	7.36	145	27	138	3.3	13
3	Velan	12152	54	m	28	1415	1	75	92	67	75.3	7.37	145	28	137	3.5	10
4	Thamaraiselvan	12168	56	m	24	1395	1	72	96	61	72.7	7.34	185	29	131	3.4	12
5	Kalian	12180	57	m	23	1375	1	76	98	58	71.3	7.38	195	29	134	3.3	11
6	Senkathir	12196	59	m	26	1330	1	74	95	54	67.7	7.37	124	29	135	3.5	12
7	Venkatesh	12199	23	m	25	1190	1	72	96	62	73.3	7.36	154	28	136	3.6	10
8	Muthulakshmi	12201	35	f	21	1435	1	74	95	61	72.3	7.35	154	26	135	3.5	9
9	Dhanalakshmi	12209	46	f	23	1185	1	74	94	68	76.7	7.39	154	29	136	3.6	10
10	amutha	12220	56	f	25	1360	1	75	90	62	71.3	7.35	145	31	134	3.2	10
11	Mukesh	12234	57	m	29	1260	1	78	88	65	72.7	7.32	145	30	132	3.3	12
12	Amaravathy	12248	52	f	28	1305	2	74	95	61	72.3	7.5	145	30	136	3.1	12
13	Kathiravan	12260	54	m	26	1215	1	77	91	54	66.3	7.36	147	29	136	3.2	13
14	Kavitha	12289	34	f	22	1205	1	78	95	55	68.3	7.33	147	28	135	3.5	10
15	Anand	12421	32	m	21	1335	1	84	85	59	67.7	7.34	145	28	135	3.6	10
16	Pandeeswari	12560	43	f	19	1120	1	95	95	58	70.3	7.36	168	29	134	3.5	9

ONE HR AFTER MANNITOL ADMINISTRATION

S.No.	Name	IP No.	age	sex	bmi	Urine(ml)	***relaxation score***	***HR***	***SYST BP***	***DIAST BP***	***MAP***	***PH***	PO2	PCO2	***sodium***	***pottasium***	***anion gap***
1	Mariappan	11258	22	m	23	535	4	67	134	90	104.67	7.35	154	29	138	4.1	14
2	Selva raj	11320	32	m	24	610	4	68	140	101	114.00	7.36	152	30	135	4.2	13
3	Ilayaraja	11345	35	m	22	605	4	84	136	96	109.33	7.37	140	30	136	3.6	15
4	Prakash	11360	38	m	28	505	3	85	140	86	104.00	7.42	152	28	138	3.4	16
5	Fatima	11378	45	f	26	455	3	74	142	90	107.33	7.35	156	26	145	3.5	12
6	Pandeeswari	11425	49	f	20	585	3	84	134	110	118.00	7.38	145	26	135	3.6	14
7	Kalaiselvan	11446	52	m	34	540	3	92	145	98	113.67	7.34	150	26	144	3.5	15
8	Kumaran	11449	53	m	25	480	4	92	140	100	113.33	7.42	158	24	132	4.3	41
9	Raja	11528	55	m	26	630	4	70	140	105	116.67	7.46	156	23	135	3.8	15
10	Dhanalakshmi	11569	34	f	21	490	4	68	145	108	120.33	7.36	142	29	144	3.7	11
11	amutha	11635	44	f	22	500	3	65	135	90	105.00	7.36	152	23	135	3.5	13
12	Sukumar	11639	34	m	28	620	3	75	142	92	108.67	7.39	142	31	145	3.4	13
13	Rajan	11700	23	m	29	485	4	84	132	102	112.00	7.38	142	28	144	3.6	14
14	Brindha	11712	34	f	25	560	4	72	130	100	110.00	7.35	147	29	132	3.2	15
15	Mandaiyan	11715	45	m	27	600	4	71	130	96	107.33	7.36	142	25	136	3.6	12
16	Kaliappan	11768	56	m	26	510	4	70	125	105	111.67	7.42	152	28	139	3.9	13
group b																	
1	gurunathan	11789	23	m	23	1120	3	56	136	90	105.33	7.36	145	33	133	4.2	12
2	Selvan	11800	34	m	24	940	3	58	135	94	107.67	7.35	165	26	136	3.5	13
3	Ganapathy	11804	35	m	25	1085	2	92	132	98	109.33	7.33	145	30	135	4.3	16
4	Guruvan	11836	45	m	26	970	3	78	136	92	106.67	7.31	145	30	132	3.9	15
5	alagarsamy	11842	46	m	23	1040	3	84	128	97	107.33	7.32	185	32	135	3.7	14
6	Sindhu	11856	56	f	21	965	3	82	130	96	107.33	7.35	196	25	142	3.6	12

7	Ilakkiya	11860	57	f	22	1060	3	84	143	91	108.33	7.35	158	30	135	3.8	13
8	Muthulakshmi	11869	60	f	25	865	3	81	135	101	112.33	7.36	157	29	134	3.4	15
9	Chinathai	11921	26	f	26	885	3	76	135	92	106.33	7.38	165	24	136	3.9	14
10	Phelix rani	11935	27	f	24	925	3	75	153	95	114.33	7.38	185	27	139	4.5	12
11	Sharmila Devi	11944	28	f	23	1050	3	78	130	96	107.33	7.33	147	29	135	4.6	12
12	Parvathi	11956	29	f	21	890	3	82	145	93	110.33	7.41	145	29	138	4.5	12
13	Sudalai	11978	30	m	22	1075	2	78	135	94	107.67	7.39	148	28	136	4.3	13
14	Shanthi	11990	35	f	21	860	3	81	135	105	115.00	7.37	149	27	135	4.1	16
15	alagar	11994	36	m	20	920	3	76	132	94	106.67	7.35	147	23	134	4.2	15
16	Baskaran	12003	37	m	22	900	3	82	130	95	106.67	7.41	124	29	132	4.1	14
group c																	
1	Karuppu	12009	32	m	25	1610	1	65	92	55	67.33	7.32	165	24	134	3.2	9
2	Kumar	12056	43	m	26	1550	1	62	88	63	71.33	7.31	154	26	136	3.3	13
3	Velan	12152	54	m	28	1535	1	62	86	45	58.67	7.37	145	28	137	3.5	10
4	Thamaraiselvan	12168	56	m	24	1670	1	65	96	61	72.67	7.34	146	29	131	3.4	12
5	Kalian	12180	57	m	23	1655	1	68	98	62	74.00	7.38	174	25	134	3.3	11
6	Senkathir	12196	59	m	26	1555	1	64	95	54	67.67	7.37	185	29	135	3.5	12
7	Venkatesh	12199	23	m	25	1575	1	62	96	62	73.33	7.33	196	28	136	3.5	10
8	Muthulakshmi	12201	35	f	21	1780	1	68	95	61	72.33	7.35	169	26	135	3.5	9
9	Dhanalakshmi	12209	46	f	23	1600	1	74	94	62	72.67	7.39	158	29	136	3.6	10
10	amutha	12220	56	f	25	1580	1	68	90	62	71.33	7.35	147	24	134	3.2	10
11	Mukesh	12234	57	m	29	1635	1	81	90	65	73.33	7.32	147	30	132	3.3	12
12	Amaravathy	12248	52	f	28	1590	***1***	64	95	61	72.33	7.32	158	30	136	4.1	12
13	Kathiravan	12260	54	m	26	1625	1	72	91	54	66.33	7.36	169	25	136	3.2	13
14	Kavitha	12289	34	f	22	1735	1	74	95	55	68.33	7.33	158	28	135	3.5	10
15	Anand	12421	32	m	21	1560	1	74	88	59	68.67	7.34	147	28	135	3.6	10
16	Pandeeswari	12560	43	f	19	1710	1	75	95	58	70.33	7.36	174	26	134	3.5	9

Ref.No.4459/E1/5/2014

Madurai Medical College,
Maduai -20. Dated: 27.05.2014.

Institutional Review Board/Independent Ethics Committee
Capt.Dr.B.Santhakumar,MD (FM). deanmdu@gmail.com
Dean, Madurai Medical College &
Government Rajaji Hospital, Madurai 625 020 . Convenor

Sub: Establishment – Madurai Medical College, Madurai-20 – Ethics Committee Meeting – Meeting Minutes - for May 2014 – Approved list – reg.

The Ethics Committee meeting of the Madurai Medical College, Madurai was held on 12th May 2014 at 10.00 Am to 12.00 Noon at Anaesthesia Seminar Hall at Govt. Rajaji Hospital, Madurai . The following members of the Ethics Committee have attended the meeting.

1.Dr.V.Nagarajan,M.D.,D.M(Neuro) Ph: 0452-2629629 Cell No.9843052029 nag9999@gmail.com.	Professor of Neurology (Retired) D.No.72, Vakkil New Street, Simmakkal, Madurai -1	Chairman
2.Dr.Mohan Prasad, MS.M.Ch. Cell.No.9843050822 (Oncology) drbkcmp@gmail.com	Professor & H.O.D of Surgical Oncology (Retired) D.No.32, West Avani Moola Street, Madurai.-1	Member Secretary
3.Dr.K.Parameswari, MD(Pharmacology) Cell No.9994026056 drparameswari@yahoo.com.	Director of Pharmacology Madurai Medical College.	Member
4.Dr.S.Vadivel Murugan, MD., (Gen.Medicine) Cell No.9566543048 svadivelmurugan_2007@rediffmail.com.	Professor & H.O.D of Medicine Madurai Medical College	Member
5. Dr.L.Santhanalakshmi, MD (Physiology) Cell No.9842593412 dr.l.santhanalakshmi@gmail.com.	Vice Principal, Prof. & H.O.D. Institute of Physiology Madurai Medical College	Member
6.Dr.A.Sankaramahalingam, MS., (Gen. Surgery) Cell.No.9443367312 chandrahospitalmdu@gmail.com	Professor & H.O.D. Surgery Madurai Medical College. Madurai	Member
7.Mrs.Mercy Immaculate Rubalatha, M.A., Med., Cell.No.9367792650 lathadevadoss86@gmail.com	50/5, Corporation Officer's Quarters, Gandhi Museum Road, Thamukam, Madurai-20.	Member
8.Thiru.Pala.Ramasamy, B.A.,B.L., Cell.No.9842165127 palaramasamy2011@gmail.com	Advocate, D.No.72,Palam Station Road, Sellur, Madurai-20.	Member
9.Thiru.P.K.M.Chelliah, B.A., Cell No.9894349599 pkmandco@gmail.com	Businessman, 21 Jawahar Street, Gandhi Nagar, Madurai-20.	Member

The following project was approved by the committee

Name of the PG Student	Course	Name of the project	Remarks
Dr.K. Prasanna drprasanna.29@gmail.com	PG in MD., (Anaesthesia), Institute of Anaesthesiology, Madurai Medcial College and Govt. Rajaji Hospital, Madurai-20.	A Comparison of three doses of Mannitol on brain relaxation during supratentorial brain tumor craniotomy: A randomized trial.	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain it confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution or to Government.
2. She/He should inform the institution Ethical Committee, in case of any change of study procedure, site and investigation or guide.
3. She/He should not deviate the area of the work for which applied for Ethical clearance. She/He should inform the IEC immediately, in case of any adverse events or Serious adverse reactions.
4. She/He should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and if any Extension of time is required He/She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the E thical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the work or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

Chairman
Ethical Committee

for 27/5/2014
Member Secretary
Ethical committee

27.5.14
DEAN/Convenor
Madurai Medical College & Govt.
Rajaji Hospital, Madurai- 20.

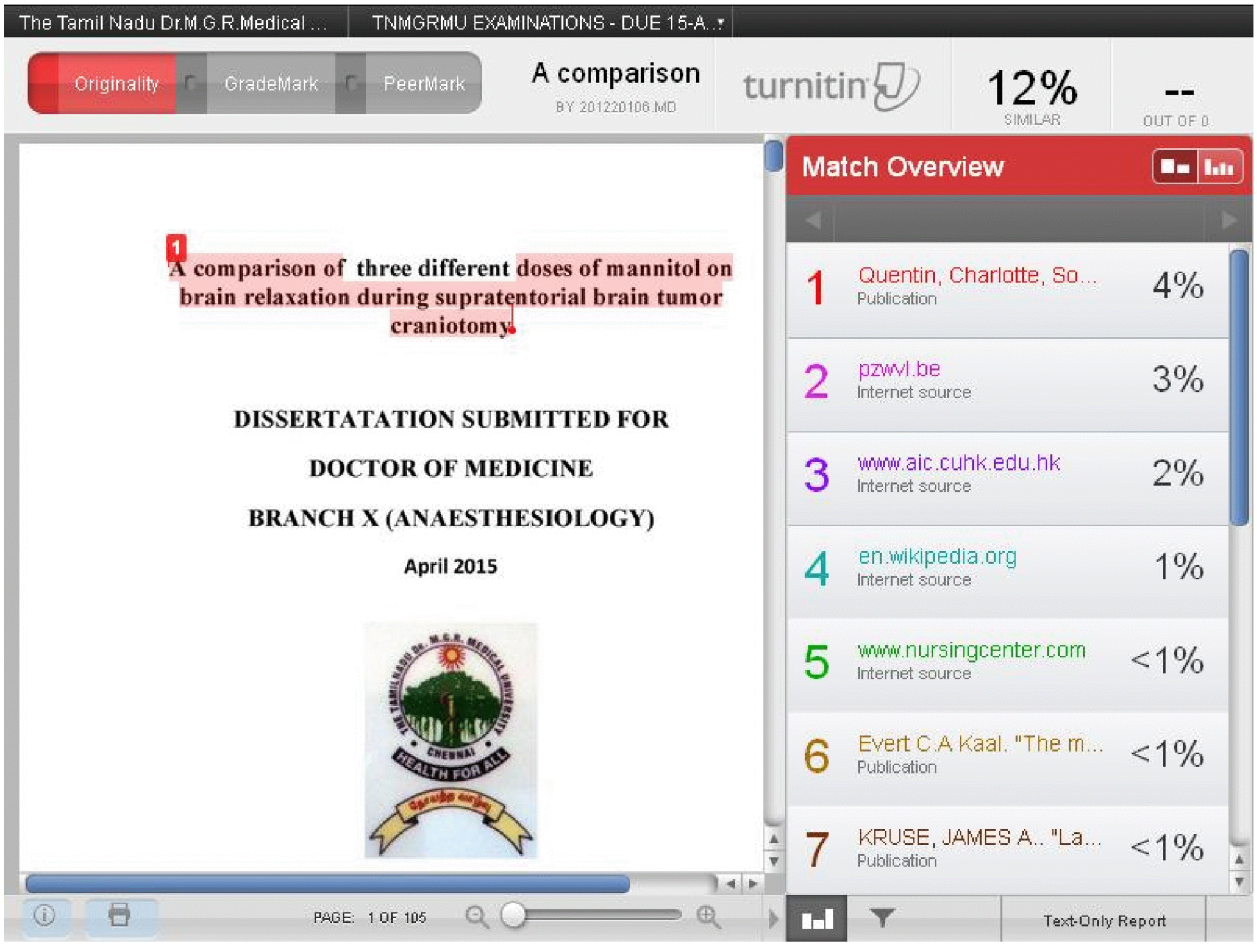
27/5/14

To
The above Applicant
-thro. Head of the Department concerned

forward to Dr. Prasanna

The following project was approved by the committee

DIRECTOR
INSTITUTE OF ANAESTHESIOLOGY
Madurai Medical College &
Govt. Rajaji Hospital
Madurai-625 020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DISSERTATATION SUBMITTED FOR
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BRANCH X (ANAESTHESIOLOGY)
April 2015
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